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Archives of Internal Medicine

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STUDIES ON THE VISCERAL SENSORY NERVOUS SYSTEM

XIV. THE REFLEX CONTROL OF THE CARDIA AND LOWER ESOPHAGUS IN MAMMALS *

A. J. CARLSON, PH.D., M.D.; T. E. BOYD, AND J. F. PEARCY

CHICAGO

LITERATURE

The literature on the reflex control of the cardia and lower esophagus is rather meager, in view of the importance of this question in connection with spasms of the cardia and esophagus in man. Most of the work has been done in connection with the deglutition and vomiting acts.

It was reported in a previous communication that the cardia and the lower end of the esophagus are provided with motor and inhibitory efferents both via the vagi and the splanchnic nerves.[1] We now know that in the swallowing act the vagi efferents are controlled by afferent impulses both from the pharynx (primary peristalsis) and the wall of the esophagus (secondary peristalsis).[2] Furthermore, the cardia and the part of the esophagus made up of smooth musculature and Auerbach's nervous plexus are capable of local coordination, that is, local automatism or reflex action, independent of afferent and efferent connections with the central nervous system.[3] There has been no important contribution to the analysis of this phase of the swallowing act since the review of the subject by Cannon in 1911. But Alvarez [4] has recently attempted to explain most, if not all, the motor phenomena of the intestine on the basis of a purely muscular gradient of rhythmicity, denying local reflexes in the intestine itself, and minimizing the importance of the extrinsic nerves in the control of the intestine. The rôle of the splanchnic efferents in deglutition, however, has not been studied.

* From the Hull Physiological Laboratory of the University of Chicago.

1. Carlson: Am. J. Physiol. **60**:14, 1922. Carlson and Luckhardt: Am. J. Physiol. **57**:299, 1921.

2. Meltzer: Am. J. Physiol. **2**:266, 1899; Zentralbl. f. Physiol. **19**: 1905.

3. Cannon: Am. J. Physiol. **19**:436, 1907. The Mechanical Factors of Digestion, New York, 1911.

4. Alvarez: The Mechanics of the Digestive Tract, New York, 1922.

The reflex relation of the glossopharyngeal afferents to the esophagus is complex. Kronecker and Meltzer [5] report that section of this nerve in animals leads to hypertonus of the esophagus lasting as long as twenty-four hours, while stimulation of the central end of the nerve may inhibit, instead of initiate, the swallowing act. Kitajew [6] found that weak stimulation of the glossopharyngeal nerve inhibited deglutition, while strong stimulation had the opposite effect. Valenti,[7] working on dogs without anesthesia, reports that cocainizing (from 6 to 50 per cent.) the pharynx alone, or the esophagus down to the cardia, leads to such strong and prolonged spasm of the cardia that strong efforts at vomiting induced by apomorphin cannot force food into the esophagus. Cocainizing the vagi trunks in the neck also prevents expulsion of food by vomiting. Stimulation of the glossopharyngeal nerve, on the other hand, may induce dilation of the cardia and vomiting, with expulsion of the food from the stomach. Kronecker and Meltzer [8] found, in man, that carbonated water in the stomach induces strong and prolonged spasm of the cardia that cannot be inhibited by deglutition. This cardiospasm is felt as a painful cramp. V. Mikulicz [9] reported (man) that mechanical or chemical irritation of the mucosa in the region of the cardia likewise induces hypertonus of the cardia. Carbonated water and cold water in the esophagus also tend to cause hypertonus of the cardia. Cannon,[3] working on cats, and using both the roentgen ray and the Langley method for observing the tonus of the cardia, reports that acid on the stomach side increases the tonus of the cardia and thus prevents regurgitation of food into the esophagus during gastric digestion contractions. This influence of gastric acidity on the cardia obtains after section of the vagi and the splanchnic nerves. Cannon therefore regards it primarily as a local reflex.

Palugyay [10] reports (man) that barium-milk passes more slowly through the cardia when the stomach is already partly filled with the mass. This may indicate that the tonus of the cardia is increased reflexly by tension in the walls of the stomach.

Openchowski [11] reports reflex dilatation of the cardia by stimulation of the kidneys, the uterus, the urinary bladder and the sciatic nerve. He also obtained dilatation of the cardia on stimulation of the motor area of the cerebral cortex.

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5. Kronecker and Meltzer: Monatschr. d. Preuss. Akad. d. Wissensch., 1881, p. 100.
6. Kitajew: (Thesis, Russian) quoted from Jahresb. u. d. Fortschr. d. Physiol., 1908, p. 151.
7. Valenti: Zentralbl. f. Physiol. **20**:449, 1906; Arch. f. Exper. Pathol. u. Pharmakol. **63**:118, 1910.
8. Kronecker and Meltzer: Arch. f. Physiol., 1883, Suppl. B, p. 355.
9. Von Mikulicz: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **12**:569, 1903.
10. Palugyay: Arch. f. d. ges. Physiol. **187**:233, 1921.
11. Openchowski: Zentralbl. f. Physiol. **3**:1, 1889; Arch. f. Physiol., 1889, p. 349.

Since the tonus of the cardia appears to be closely correlated to that of the stomach, we must take into account the reflex control of the latter organ in connection with the cardia. Wertheimer [12] found that sciatic stimulation caused inhibition of the stomach. This reflex was decreased by section of the vagi, but not entirely abolished by subsequent section of both the splanchnic nerves. Morat [13] obtained inhibition of the stomach on stimulation of the central end of one vagus, provided the other vagus remained intact. Auer,[14] working on rabbits, describes reflex gastric inhibition from chemical and mechanical irritation of the nasopharynx, and by irritation of the splanchnic afferents. Auer concluded that the vagi constitute the principal efferent path in this reflex. Barber and Stewart [15] have recently reported contraction of the stomach (dog) from stimulation of the appendix, the gallbladder, and the duodenum.

As regards the tonus and contractions of the empty stomach (man, dog, not under anesthesia), we showed nine years ago that these are inhibited by chemical and mechanical stimulations of the nerve endings in the mouth as well as in the gastric mucosa.[16] We were not able by any means to induce reflex hypertonus or contractions of the stomach in normal men and dogs by such stimuli as could be used without general anesthesia.[17]

EXPERIMENTAL METHODS

The methods used in this work are essentially the same as described in the report on the innervation of the mammalian cardia,[1] and the reader is referred to that paper for a more detailed description and criticism both of the mechanical devices for recording the cardia contractions and the methods of preparing the animals for experimentation. For the convenience of the reader, Figure 1 of that report is reproduced here, showing in diagram the position of the cardiometer and the devices for keeping it in place.

The animals used were cats and dogs.

One dog was provided with a permanent gastrostomy and esophageal fistula in the neck. This animal was dressed daily and otherwise well cared for, so that he is in first class condition. This dog was used for the study of reflexes to the cardia from the mouth, pharynx, and stomach, action of cocain on the cardia, etc., without anesthesia.

12. Wertheimer: Arch. de Physiol. **4**:379, 1891.
13. Morat: Arch. de Physiol. **5**:142, 1893.
14. Auer: Am. J. Physiol. **18**:347, 1907; ibid. **25**:334, 1910.
15. Barber and Stewart: Proc. Soc. Exper. Biol. & Med. **17**:155, 1920.
16. Carlson: Am. J. Physiol. **31**:212, 1913; ibid. **32**:389, 1913.
17. Carlson: Am. J. Physiol. **35**:155, 1914. The Control of Hunger in Health and Disease, Chicago, 1916.

In all the acute experiments the animals were anesthetized with ether. Gastrostomy and fistula of the esophagus were made for fixing the cardiometer in place. Usually a balloon was also placed in the stomach for recording the gastric tonus. From here on the following procedures were used:

1. The experiment was conducted under constant, but light, ether anesthesia.

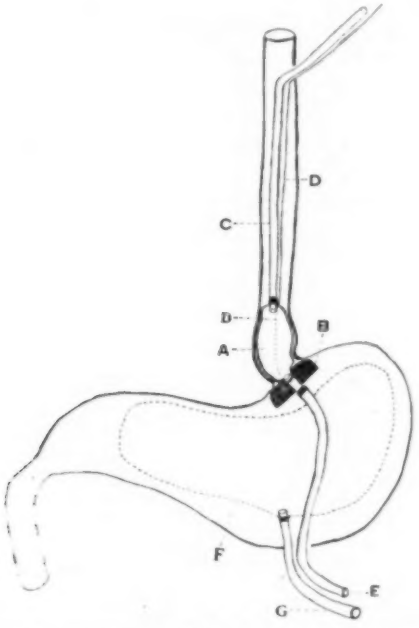

Fig. 1.—Diagram to illustrate method of continuous recording of the tonus of the cardia. A, (condom from 4 to 6 cm. in length) in cardia and lower esophagus. B, Rubber plug (from 2 to 2.5 cm. diameter, 1 cm. thick), preventing cardia balloon from being pushed or pulled up into esophagus. C, Rubber tube (4 mm. diameter), connecting esophageal end of cardia balloon with water manometer via esophageal fistual in neck. D, thread passing inside cardia balloon and firmly attached to rubber plug (B) for holding balloon (A) in cardia. E, rubber tube (4 mm. diameter) connecting stomach end of cardia balloon with water manometer through gastric fistula. F, balloon (condom, length from 10 to 15 cm.) in stomach. G, rubber tube connecting gastric balloon with water manometer through gastric fistula.

2. Ether anesthesia was continued with curare (crude extract) and artificial respiration, for elimination of skeletal and respiratory reflexes.

3. Animals were decerebrated and the ether anesthesia discontinued.

4. Conditions 1, 2 and 3 were followed with chest and respiratory mechanism intact, or with chest opened, artificial respiration, the phrenic

nerves sectioned and the diaphragm dissected away from the esophagus as completely as possible without injury to the innervation of the cardia and lower esophagus. This procedure eliminates possible errors in the tracings from contraction or spasm of the diaphragm. But it has the drawback of decreasing reflex action from "shock" due to the extensive dissection or trauma.

The following criticism may be made against procedures 1, 2 and 3.

(a) Anesthesia of sufficient depth to abolish pain and skeletal movements depresses at the same time the reflexes to the cardia. Under deep anesthesia (abolition of the lid reflex) reflexes into the cardia are abolished, or are feeble and inconstant. It is, therefore, probable that positive results under anesthesia, while correct qualitatively, are subnormal in quantity, that is, in strength and duration. But one might even question whether they are necessarily correct in quality, since ether anesthesia lowers the tonus of the cardia, and we have shown that the quality of the primary response of the cardia to stimulation of the extrinsic efferents depends on the degree of tonus of the cardia at the moment of stimulation.

(b) The anesthesia factor can be eliminated by decerebration, but handling of the visceral organs and stimulation of visceral afferents in good decerebrate preparations induces violent and prolonged skeletal movements with ultimate depression of all reflexes ("shock"). When general body movements are violent and the respiratory movements are irregular, the recording of the cardia tonus by the present method is rendered difficult.

(c) From the above considerations it would seem that the ideal preparation would be decerebration combined with curare and artificial respiration. We found, however, that crude extract of curare (Merck) in doses sufficient to paralyze the skeletal muscles for from fifteen to twenty minutes, has a direct stimulating action on the cardia and lower esophagus, inducing spasms of these regions lasting from three to fifteen minutes, and for some time after such spasm the cardia reflexes are depressed. The stronger the dose of curare the more prolonged the spasm of the cardia. And since minimal doses of curare, in cats, must be repeated every twenty or thirty minutes, curare does not leave the cardia mechanism even approximately normal. Furthermore, Klee [18] reports that decerebration in cats increases the tonic action on the intestine both of the vagi and the splanchnic nerves, the former predominating.

We have obtained definite reflexes into the cardia in curarized, in decerebrated, and in curarized and decerebrated preparations, but light ether anesthesia alone yielded, on the whole, better results.

18. Klee: Deutsch. Arch. f. klin. Med. **129**:275, 1919.

The experiments that we were able to make on the dog with the permanent gastrostomy and esophageal fistula, without anesthesia, are physiologic, both in quality and quantity, as this animal was normal and in first class condition.

RESULTS

A. *Cardia Reflexes From Skeletal Afferents.*—When both vagi and the splanchnic nerves are intact, stimulation of the central end of the

Fig. 2.—Cat. Light ether anesthesia. Stomach in state of digestion, but food removed through gastrostomy. Cardia and lower esophagus hypertonic, with rhythmical contractions. Water manometer tracings. A, cardia end of cardiometer. B, esophageal end of cardiometer. Signal, tetanization of central end of sciatic nerve. Showing reflex inhibition of the hypertonic cardia. Time, minutes.

sciatic nerve with the tetanizing current usually produces inhibition of the tonus of the cardia and the lower esophagus (Fig. 2), as reported by Openchowski. This is particularly true if the cardia is in strong tonus. But in some experiments contraction of the cardia followed the sciaic stimulation. Both the contractions and the inhibitions usually last for a considerable period beyond the stimulation.

When both vagi are sectioned in the neck, sciatic stimulation usually causes a prolonged spasm or contraction of the cardia (Fig. 3).

We have shown that, in the cat, epinephrin usually causes contraction, but it may also cause inhibition of the cardia. The question whether strong sciatic stimulation leads to an increased output of epinephrin is in dispute. But epinephrin is, at least, not solely responsible for the cardia effects here described, for they can be obtained after excision of the suprarenals. It is true that after complete suprarenalectomy the cardia reflexes induced by sciatic stimulation are usually

Fig. 3.—Cat. Light ether anesthesia. Both vagi sectioned, chest opened. Artificial respiration. Both phrenic nerves sectioned. Water manometer tracings. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. Signal, tetanization of central end of sciatic nerve. Showing reflex spasm of the cardia via the splanchnic motor efferents. Time, minutes.

less marked. But we are inclined to ascribe this to depression of the reflex centers (central and peripheral) from the trauma of the operation.

B. *Cardia Reflexes From the Mouth and Pharynx.*—In cats under light anesthesia mechanical, chemical, or thermal stimulation of the tongue and mouth inhibits the tonus of the cardia (Fig. 4). The inhibition may be followed by increased tone at the end of the stimulation. These effects are independent of deglutition. We have obtained similar

inhibition of the cardia from the mouth in our fistula dog, but in a dog not under anesthesia it is difficult to stimulate the tongue or the mouth in any way without inducing swallowing from the increased salivation.

If the cardia is atonic, mechanical stimulation of the pharynx usually causes contraction of the cardia and lower esophagus. If the cardia is in strong tone the stimulation causes primary inhibition followed by contraction (Fig. 4). Similar effects are produced by tetanization of the central end of the glossopharyngeal nerve. These reflexes are obtained in the absence of swallowing, but they fail after section of both vagi nerves.

After finding that mechanical stimulation of the pharynx, that is, of the glossopharyngeal nerve field, or tetanization of the central end of the cut glossopharyngeal nerve itself, induces opposite cardia reflexes, depending on the tonus of the cardia, we became interested in the findings of Kronecker and Meltzer, and of Valenti, that section of these nerves, or cocainization of the pharyngeal mucosa induces permanent (many hours) hypertonus of the cardia. In acute experiments on cats we have not been able to secure the permanent hypertonus of the cardia and esophagus described by Kronecker and Meltzer as following section of both glossopharyngeal nerves. This operation cannot be made complete without some mechanical injury to the root of the vagi. Hence temporary motor disturbance of the cardia and esophagus following section of both glossopharyngeal nerves under anesthesia may be due to disturbance of the vagi.

We have repeated the experiments of Valenti of cocainizing the pharynx of cats, under anesthesia. This procedure usually leads to some hypertonus of the cardia as reported by Valenti. But we are not satisfied that Valenti's interpretation of the fact is adequate. In the first place, it is not possible, even in light anesthesia, to cocainize the pharynx without some of the drug reaching the esophagus, and possibly even the cardia, even when the animal does not swallow. Valenti used strong solutions of the drug (from 6 to 50 per cent.). Under such conditions some of the cocain will be absorbed from the pharynx and esophagus into the general circulation and may act on the cardia via the blood.

It is known that cocain, in the blood, increases the action of visceral nervous mechanisms.[19] We have seen that the cardia and lower esophagus have motor innervation via the splanchnic system. Numerous experiments were made on cats under ether anesthesia, and on the dog with the permanent fistulae to test this possibility of direct action of cocain on the cardia. Intravenous injection of as little as 1 mg. cocain

19. Tatum: J. Pharmacol. & Exper. Therap. **16**:109, 1920.

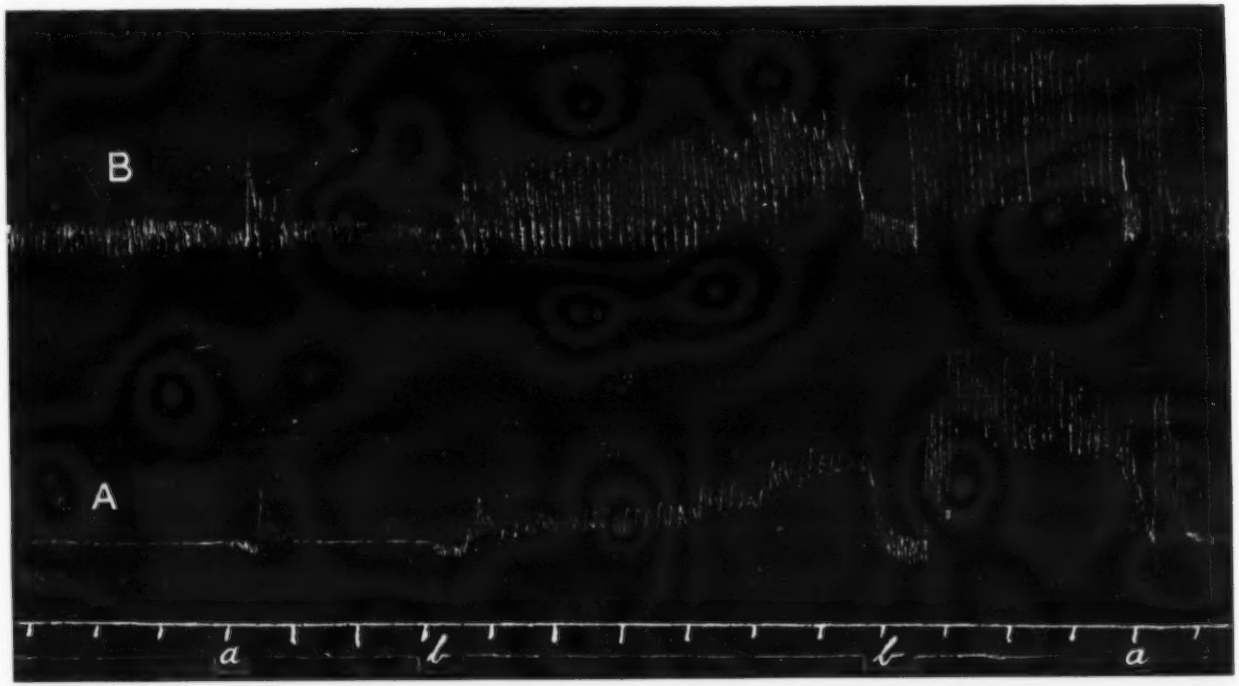

Fig. 4.—Cat. Ether anesthesia. Vagi and splanchnic nerves intact. Water manometer record. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. Signal *a*, mechanical stimulation of the tongue; *b*, mechanical stimulation of the pharyngeal mucosa. Showing reflex inhibition and contraction of the cardia and esophagus from the mouth and pharynx. Time, minutes.

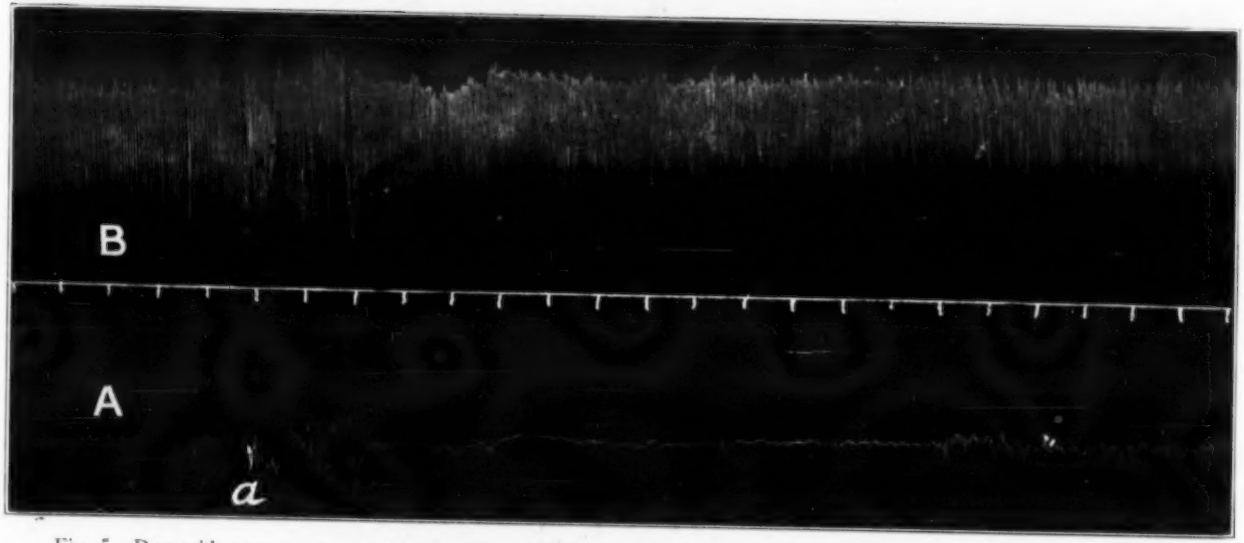

Fig. 5.—Dog with permanent gastrostomy and esophageal fistula. No anesthesia. Stomach empty. Water manometer tracing. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. *a*, intravenous injection of 1 mg. cocain. Showing increased tonus of cardia from cocain. Time, minutes.

in the cat, and from 1 to 2 mg. in the 15 kg. dog induces distinct hypertonus of the cardia, lasting from five to fifteen minutes (Fig. 5). Larger doses of the drug have more pronounced effects.

Since stimulation of the glossopharyngeal nerve induces both inhibition and contraction of the cardia via the vagi efferents, and as cocain in the blood has a direct motor action on the cardia it is evident that hypertonus of the cardia following cocainizing of the pharynx is not due solely to the elimination of afferent impulses via the glossopharyngeal nerve that maintain the vaguscardia inhibitory tonus in the normal animal.

Fig. 6.—Cat. Light ether. Water manometer tracings. A, balloon in lower esophagus and cardia. B, balloon in esophagus at level of heart. *a*, traction on right vagus by pulling on right carotid artery, inducing spasm of the cardia.

C. *Cardia Reflexes via the Vagi Afferents.*—The cardia and lower esophagus in cats, even under ether anesthesia, are very sensitive to mechanical stimulation of the vagi trunks in the neck. The prevailing effects of traction on the intact vagus by pulling on the carotid artery is a spasm of the cardia and lower esophagus (Fig. 6). This is probably partly due to mechanical stimulation of the motor fibers in the vagi, and is in part a reflex via the vagi afferents. Section of the vagi produces similar spasm of the cardia (Fig. 7). If one vagus is left intact stimula-

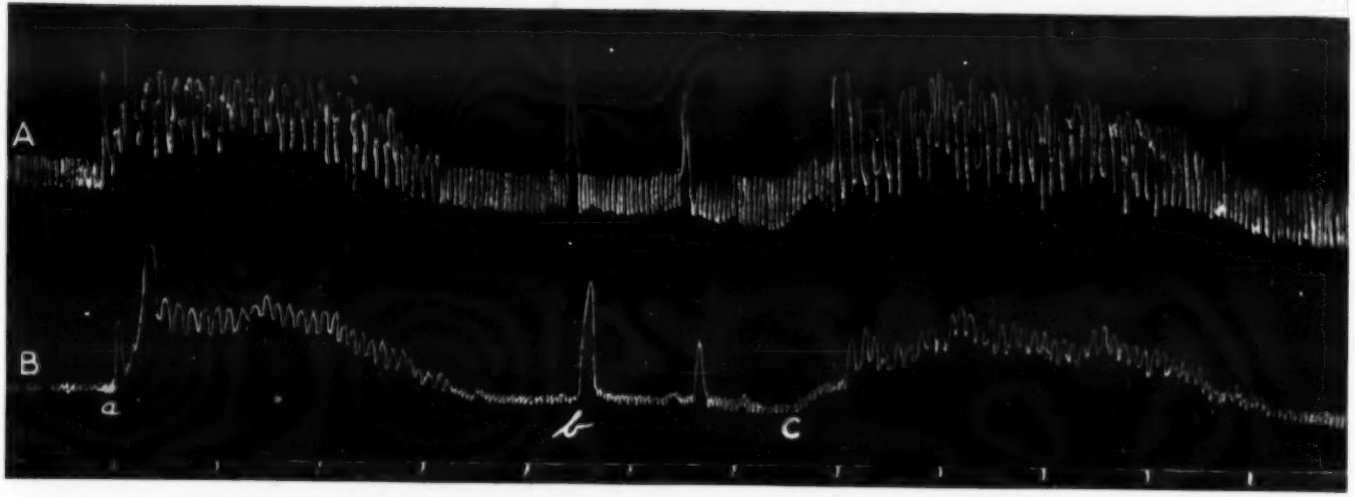

Fig. 7.—Cat. Light ether anesthesia. A, record from cardia opening of cardiometer. B, record from esophageal opening of cardiometer. *a*, section of left vagus in the neck. *b*, beginning isolation of right vagus in neck. *c*, section of right vagus. Showing temporary spasms of lower esophagus and cardia, following section of the vagi (motor effects). Time, minutes.

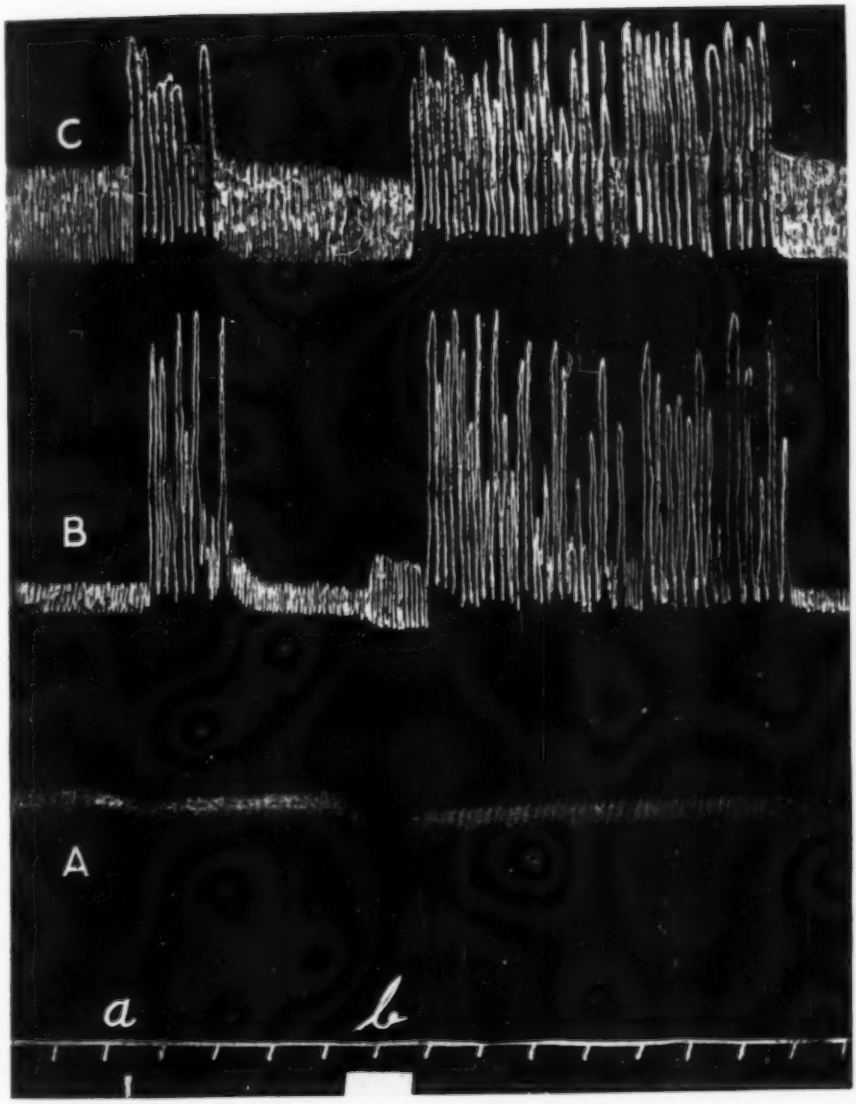

Fig. 8.—Decerebrated cat. Water manometer tracings. Left vagus sectioned in the neck. A, balloon in stomach. B, cardia opening of cardiometer. G, esophageal opening of cardiometer. *a*, mechanical stimulation of central end of left vagus; *b*, tetanization of central end of left vagus. Showing reflex inhibition and contraction of cardia, and inhibition of stomach, from stimulation of vagi afferents. Time, minutes.

tion of the central end of the other vagus usually causes a temporary inhibition of the cardia followed by a prolonged spasm (Fig. 8). This reflex usually involves inhibition of the gastric tonus.

Since the spasm of the cardia following section of the second vagus is in strength and duration similar to that induced by section of the first vagus, it is evident that this motor response is mainly due to the mechanical stimulation of the vagi motor nerve fibers to the cardia. We have shown in a previous report [1] that in exceptional cases section of both vagi (cat, rabbit) leads to spasm of the cardia lasting for several hours or throughout an acute experiment. Such results are difficult to explain except on the basis of a normal vagi-cardia inhibitory tonus. Under the anesthesia and trauma of acute experiments this central inhibitory tonus mechanism is evidently depressed, except in an occasional preparation.

In connection with Figure 7 it may be pointed out that the spasms of the cardia, induced reflexly or by direct stimulation of the motor efferents, usually appear as hypertonus with superimposed rhythmical contractions. This is especially true of spasms of the cardia induced via the vagi motor efferents. Direct stimulation of the splanchnic motor system may induce hypertonus of the cardia with less marked rhythmical pulsations. These rhythmical contractions of the hypertonic cardia were noted over sixty years ago by Basslinger,[20] and are sometimes referred to as "Basslinger's pulse."

With the corresponding vagus intact, stimulation of the central end of the recurrent laryngeal nerve induces spasm of the cardia. We assumed that this was a reflex, the afferent path being vagi sensory fibers from the esophagus and larynx, until in some preparations this stimulation caused contraction of the cardia even after section of both vagi nerves. We feel sure that these unexpected results were not caused by escape of the electrical current to the vagus trunk or directly to the esophagus. The only explanation we can suggest is that some afferent fibers from the cervical or thoracic nerves pass into the recurrent laryngeal nerve. On this assumption, the contractions of the cardia following stimulation of the central end of the recurrent laryngeal nerve, with both vagi sectioned, is a reflex through the spinal cord and the splanchnic motor fibers. We do not think that it is an "axon reflex," as that term is used by Langley, because the innervation of the lower esophagus and cardia by branches of the same motor neuron that supplies the esophageal muscles in the neck would render the normal peristalsis of deglutition impossible.

According to experiments on dogs recently reported by Tournay,[21] some sensory innervation of the hind legs reaches its peripheral distri-

20. Basslinger: Sitzungsber. Kaiserl. Akad. f. Wissensch. **38**: 1859.
21. Tournay: Compt. rend. Acad. d. sc. **173**:939, 1921.

bution via the sympathetic system. Evidently the present views of nerve components must be reinvestigated by physiologic methods.

D. *Cardia Reflexes From the Stomach.*—In cats under light ether anesthesia and in the dog with the permanent fistula sudden stretching of the stomach wall by inflation and collapse of a condom balloon in the stomach induces hypertonus or spasms of the cardia lasting from three to ten minutes (Fig. 9). This degree of distension of the empty stomach does not cause pain or distress. Similar distention of the stomach in man is felt as fullness, without distress or pain.

Our records on the dog with the permanent gastrostomy and esophageal fistula, the experiments being done without anesthesia, indicate that the hypertonicity of the cardia following sudden tension on the walls of the stomach extends to the striaed musculature of the esophagus. It is, therefore, in part, a long reflex. This esophageal hypertonus is not in evidence on our cat records, the long reflexes being probably depressed by the general anesthesia.

Water, 0.4 per cent. hydrochloric acid and 0.4 per cent. sodium carbonate at body temperature, introduced into the stomach, induce a brief relaxation, followed by a somewhat more prolonged hypertonus of the cardia (Fig. 10). There is little or no difference in the effect on the cardia from introduction of 50 to 100 c.c. of these fluids into the stomach through the gastrostomy. This applies to the fistula dog, where no anesthesia was used, as well as to cats under ether, except that deep anesthesia abolishes all effects on the cardia. The primary effect on the cardia, of water, acids, and alkalies, when introduced into the empty stomach, is the same as on the stomach itself, that is, inhibition.

On the basis of Cannon's observations I looked for greater increase in the cardia tonus from acid in the stomach as compared to equal volumes of water or alkalies. We have recorded elsewhere that gastric acidity fails to account for the hypertonus of the cardia during normal gastric digestion.[11] This cardia hypertonus persists for some time after the food has been removed and the stomach washed out with water or alkalalies. And the digestion hypertonus cannot be reproduced by introducing acids into the empty and quiescent stomach. It may also be noted in this connection that in the normal animal the tonus of the cardia parallels the gastric tonus, even when the stomach is empty.

These results on the cardia and lower esophagus parallel our earlier findings on the empty stomach of man and dog.[11] The primary effect of water, acids or alkalies, introduced directly into the stomach, is a decrease in tonus and contraction of the stomach. This "receptive relaxation" is similar to that noted by Cannon as following deglutition, except that this is primarily a local action, probably reflex.

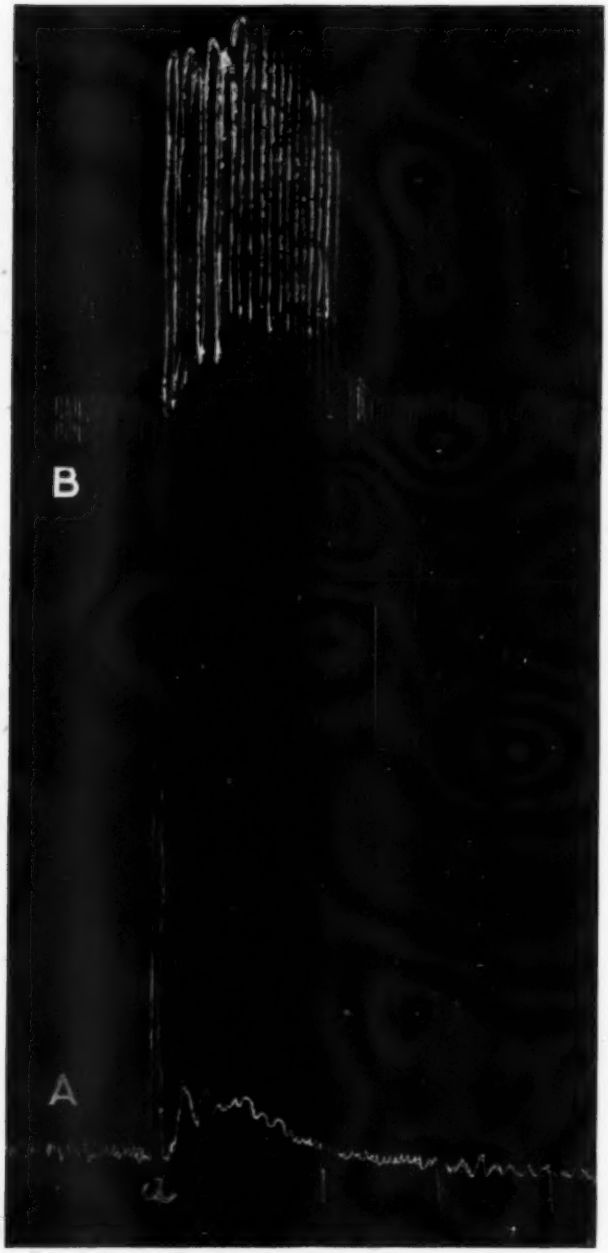

Fig. 9.—Dog with permanent gastrostomy and esophageal fistula (in the neck). Stomach empty. Water manometer tracing. A, balloon in stomach. B, cardia opening of cardiometer. C, esophageal opening of cardiometer, *a*, sudden inflation of second balloon in stomach. Showing reflex spasm of the cardia and esophagus from sudden (but temporary) distention of the stomach. Time, minutes.

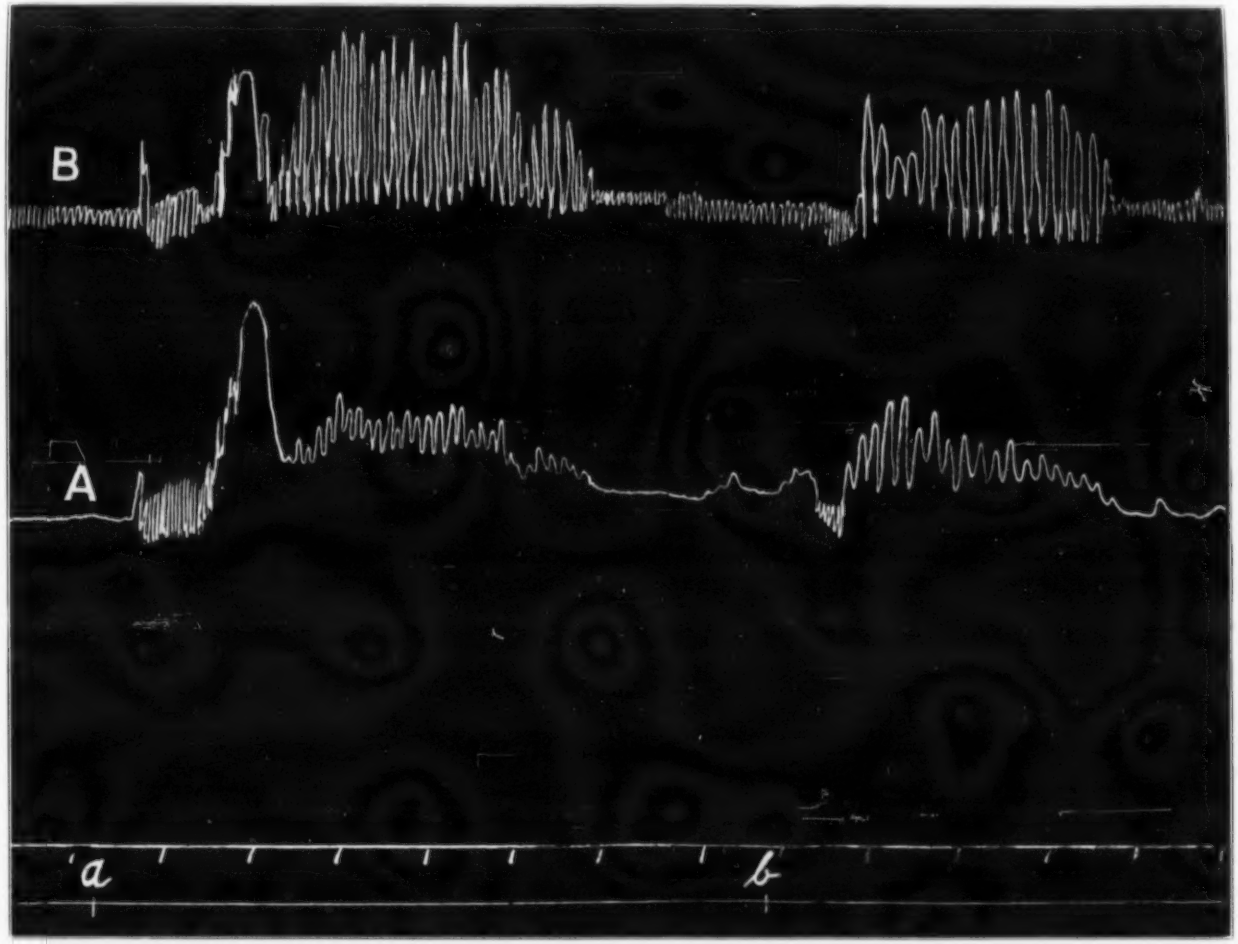

Fig. 10.—Cat, decerebrated. Cardia hypertonic. Water manometer tracing. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. *a*, 50 c.c. of water (38 C.) into the stomach; *b*, 50 c.c. 0.4 per cent. hydrochloric acid (38 C.) into the stomach. Showing primary cardia inhibition followed by a temporary hypertonus, from water and acid in the stomach. Time, minutes.

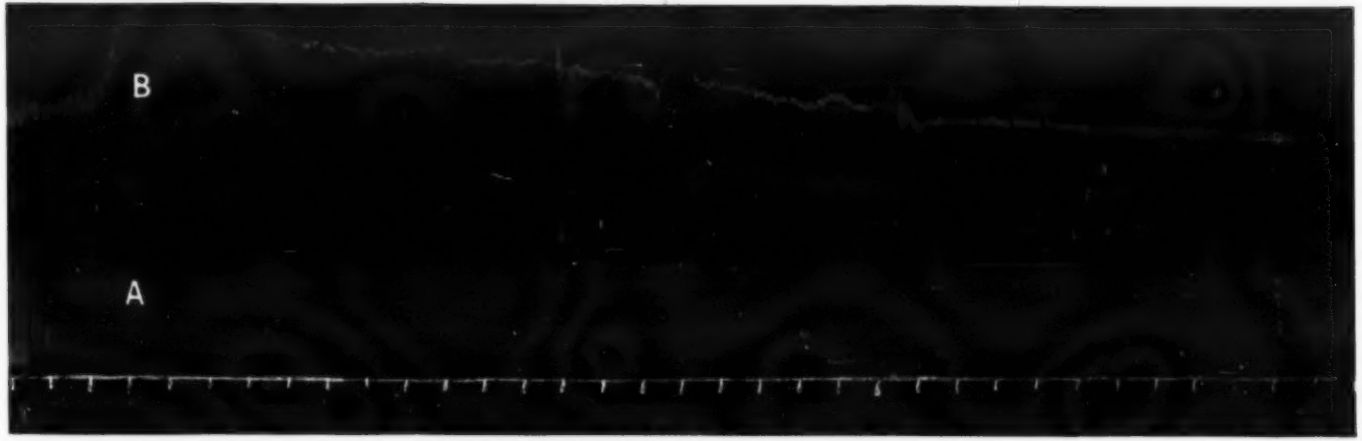

Fig. 11.—Cat. Ether anesthesia. Vagi and splanchnic nerves intact. Water manometer tracing. A, record from balloon in cardia. B, record from esophageal balloon at level of heart. ↑, pinching gallbladder with forceps. Showing prolonged reflex spasm of cardia and esophagus. Time, minutes.

F. *Cardia Reflexes From the Abdominal Viscera.*—In decerebrated cats, as well as in cats under ether anesthesia, mechanical stimulation of the gallbladder (rubbing between the fingers, pinching with forceps) or the common bile duct leads to very marked hypertonus or spasm of the cardia, lasting at times for fifteen minutes or longer (Fig. 11). This reflex is obtained, although usually in diminished degree, after section of the vagi, but not after section of both vagi and splanchnic nerves. It is, therefore, essentially a long reflex involving the vagi and splanchnic efferents. In a few experiments the gallbladder stimulation caused relaxation of the cardia. The predominance of the motor reflex

Fig. 12.—Cat. Light ether anesthesia. Water manometer tracing. A, balloon in lower esophagus and cardia. B, balloon in esophagus at level of heart. ↑, mechanical pressure on the urinary bladder, inducing spasm of the cardia.

may be due to the usual low tonus of the cardia in cats under anesthesia or shortly after decerebration. Electrical stimulation of the gallbladder is less efficient than the mechanical stimulation in producing the reflex spasm of the cardia.

Strong distension or compression (pinching, crushing) of the urinary bladder or of the large or small intestine induces predominantly cardia hypertonus or spasm outlasting for a long time the period of stimulation (Figs. 12 and 13). The splanchnic nerves are the main afferent paths, and, in part, the efferent paths for the reflex. Very

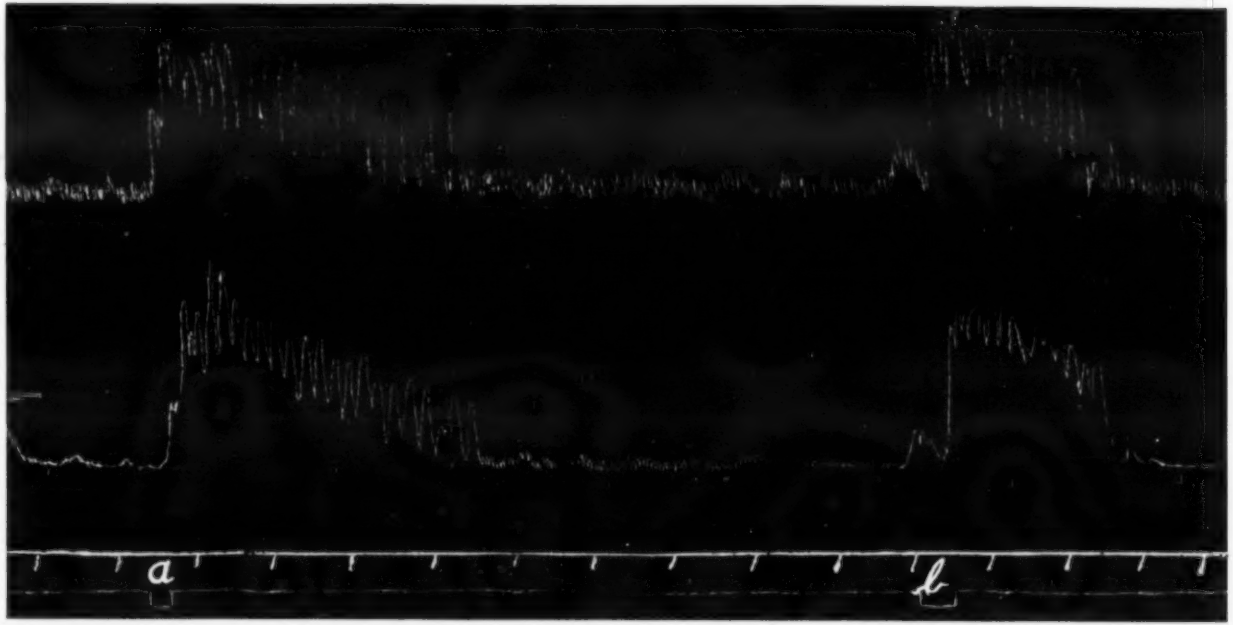

Fig. 13.—Cat. Light ether anesthesia. Water manometer tracing. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. Signal *a*, pressing duodenum between fingers; *b*, pressing large intestine between fingers. Showing reflex spasm of the cardia induced by visceral afferents. Time, minutes.

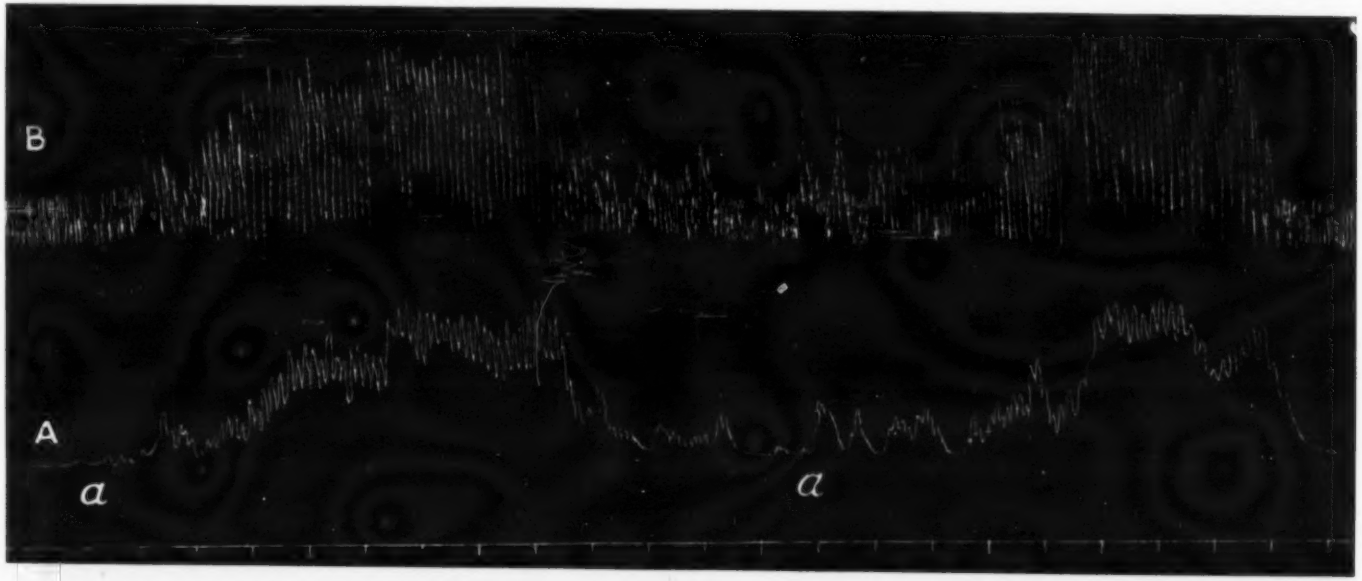

Fig. 14.—Cat. Light ether anesthesia. Water manometer tracing. A, cardia opening of the cardiometer. B, esophageal opening of the cardiometer. *a, a,* traction on the central end of the left splanchnic major (sectioned). Showing reflex spasm of the cardia induced by mechanical stimulation of the splanchnic afferents. Time, minutes.

Fig. 15.—Cat. Light ether anesthesia. Both vagi sectioned in the neck. Stomach empty. Cardia atonic. Water manometer tracing. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. *a* to *b*, isolation of left splanchnic nerves; *b*, section of left splanchnic nerve; *c*, tetanization of peripheral end of left splanchnic nerve. Showing reflex and direct motor action of the splanchnic nerve on the cardia and lower esophagus. Time, minutes.

strong reflexes into the cardia are induced by mechanical or electrical stimulation of the central end of one splanchnic nerve (Fig. 14), even after section of both vagi. The motor reflex into the cardia via the splanchnic efferents may involve stronger contraction of the cardia and lower esophagus than that caused by direct stimulation of the peripheral end of the sectional splanchnic nerve (Fig. 15).

Stimulation of the sympathetic trunk in the chest, after section of the splanchnic nerves on that side, causes hypertonus or spasm of the cardia. This result is obtained even after severance of possible efferent motor nerve fibers that may enter the cardia and lower esophagus via the aortic nerve plexus. It is therefore essentially a reflex via the visceral afferents in the thoracic sympathetic trunk.

DISCUSSION

The cardia and esophageal reflexes described in the preceding sections are complex reactions, depending not only on the condition of the central nervous system, but also on the state of the intestine. The reader must not infer that all of these reflexes can be demonstrated in a single animal, even when great care is taken with the anesthesia and the trauma of necessary dissections. In some preparations the reflexes were more readily elicited than in others, even under experimental conditions as nearly identical as possible. We have no real explanation to offer for these variations, except the unknown factor of central and peripheral "shock." The motor control of the cardia and lower esophagus involves local automatism and reflexes via the Auerbach's plexus, long reflexes via the vagi efferents, and long reflexes via the splanchnic efferents. The long reflex mechanisms can, apparently, be thrown into activity by the stimulation of any sensory nerve in the body. The response of the cardia and lower esophagus in this reflex may be either relaxation or contraction, depending in part on the state of the tonus of the cardia at the time of stimulation. If the cardia is in feeble tonus, the contraction reflex prevails; if it is in strong tonus, the inhibition reflex usually predominates. But, on the whole, in our experimental conditions in the cat and dog the inhibition reflex seems to be evoked more readily via the vagi efferents, and the motor reflex via the splanchnic efferents.

While it is true that the cerebrospinal reflexes into the cardia can be initiated by the stimulation of almost any afferent nerve, nevertheless, our results indicate that the afferents from the upper end of the alimentary tract (mouth, pharynx, esophagus) and from the viscera supplied by the splanchnic system, are in the closest reflex relation to the cardia efferents. The cardia reflexes evoked by stimulation of the sensory nerves to the mucous membrane in the mouth, the pharynx,

the esophagus and the stomach are primarily inhibitory, the cardia reflexes initiated by the splanchnic afferents are predominantly motor (spasm of the cardia).

There is a long step between these types of cardia spasm induced in normal animals, under experimental conditions, and spontaneous cardiospasms in man. There is no reason for believing that the nervous control of the cardia in man is essentially different from that in the cat. But the disturbance in the afferent side of this mechanism that may lead to spasm, may apparently occur almost anywhere in the body, particularly in the viscera. Conditions leading to hyperirritability in the regions of the medulla and thoracic cord whence the motor neurons emerge will, of course, induce spasm of the cardia by excessive activity of these efferents, provided the inhibitory efferents are not rendered hyperactive at he same time. In the latter case there should be no change in the cardia control. There is some evidence of a predominant inhibitory tone of the cardia efferents, similar to the tonic action of the vagi inhibitory efferents to the heart. On this basis, spasm of the cardia could follow depression or failure of this inhibitory tonic action. Spasms of the cardia and lower esophagus would then be similar to the tachycardia due to failure of the vagus action. This is the opposite of "vagotonia;" it is vagohypotonia. It is, of course, well known that cardiospasms occur most frequently in so-called "nervous" individuals, who frequently show other evidence of defective inhibition besides tachycardia and cardiospasm.

Chronic cardiospasm is usually associated with dilation of the esophagus (striated muscular system). This may be a further indication of vagohypotonia, as the motor nerve fibers to this musculature appear to be exclusively vagal. This is, however, not an adequate explanation in all cases, since the musculature of the dilated esophagus may show actual hypertrophy or thickening. This could not take place in failure of the motor innervation, unless the striated musculature of the esophagus is less dependent on the motor nerves than are the skeletal muscles.

The fact that, in the normal man and animal at least, the tonus of the cardia is inhibited reflexly by chemical and mechanical stimulation of the sensory nerves in the mouth, may have some practical application. Bitters or acids in the mouth may reflexly help to inhibit the milder forms of reflex cardiospasm.

SUMMARY

A. In normal dogs, not under anesthesia, it is shown that

1. The tonus of the cardia is temporarily inhibited by stimulation of sensory nerves in the mouth and pharnyx.

2. The tonus of the cardia is temporarily inhibited by stimulation of nerves in the gastric mucosa.

3. The tonus of the cardia is increased by sudden distension of the walls of the stomach.

4. The tonus of the cardia is increased by intravenous injection of small quantities of cocain.

5. The tonus of the cardia is increased during gastric digestion by some factor other than the acidity of the gastric contents.

6. The tonus of the cardia runs parallel with the tonus and hunger contractions of the empty stomach.

B. In dogs and cats under light ether anesthesia, ether and curare, or decerebration, it is shown that

1. Reflex inhibition or contraction of the cardia and lower esophagus can be initiated by the stimulation of any sensory nerve, skeletal or visceral.

2. When the vagi are intact stimulation of the sensory nerves in the mouth, pharynx, esophageal and gastric mucosa induces on the whole inhibition of the cardia, followed by contraction.

3. Stimulation of the afferents from the abdominal viscera (gall-bladder, intestine, urinary bladder, central end of one splanchnic nerve) induces on the whole reflex contraction of the cardia and lower esophagus, even when both vagi nerves are sectioned.

4. When the tonus of the cardia is feeble, the motor reflexes into the cardia predominate, when the cardia is hypertonic the inhibitory reflexes prevail.

5. Strong stimulation, particularly of the abdominal viscera or the central end of the splanchnic nerve, may cause strong spasm of the cardia and lower esophagus lasting from 10 to 30 minutes.

C. General.

1. The demonstration of motor and inhibitory innervation of the cardia and lower esophagus via the splanchnic nerves, and the confirmation and extension of Openchowski's observations on the reflex control of the cardia and lower esophagus should be taken into account in clinical cardiospasm. But it must not be inferred that the reflex spasms of the cardia here described are identical with any or all types of cardiospasm so far found in man, although it is possible that experimental chronic lesions in otherwise normal cats and monkeys may induce abnormalities in cardia control more akin to clinical cardiospasm than those revealed by the present study.

ELECTROCARDIOGRAPHY AND PROGNOSIS

I. SIGNIFICANT T WAVE NEGATIVITY IN ISOLATED AND COMBINED DERIVATIONS OF THE ELECTROCARDIOGRAM *

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Electrocardiography has been accorded distinction as a valuable diagnostic adjunct, but as yet relatively little attention has been given to its prognostic value. I have been especially interested in the study of abnormal electrocardiograms with special reference to clinical types of heart disease and the significance of these graphic changes with regard to life expectancy. In the analysis of large groups of cases of heart disease one is impressed with the frequent occurrence of certain graphic abnormalities in definite clinical types of cardiopathies. Such cases invariably present unmistakable objective evidence of high grade myocardial disease. I am referring particularly to significant T wave negativity, to aberration of the Q R S complex in all derivations of the electrocardiogram, and to the coexistence of these abnormalities. From the standpoint of prognosis, these changes constitute three well defined groups.

A very obvious fact that is brought to the attention of those who correlate large clinical and electrocardiographic data is the inability to foretell the presence or absence of these graphic changes in similarly damaged hearts.

Electrocardiography was introduced in the Mayo Clinic in 1914 and careful detailed records have been maintained of all patients examined electrocardiographically. The cases are grouped and subgrouped according to clinical and electrocardiographic types, and an automatic follow-up system of patients has been established. It is thus possible to obtain accurate mortality statistics and definitely to establish the length of life from the time of examination, and in some instances, from the onset of cardiac symptoms.

In a previous article [1] I discussed T wave negativity, its occurrence in certain isolated and combined derivations of the electrocardiogram, its occurrence in clinical types of heart disease, and the prognostic significance of certain graphic arrangements. All cases were included regardless of the association of other graphic abnormalities, particularly aberration of the Q R S complex affecting all derivations.

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* From Division of Medicine, Mayo Clinic.

1. Willius, F. A.: Observations on Negativity of the Final Ventricular T Wave of the Electrocardiogram, Am. J. M. Sc. **160**:844, 1920.

It is my intention in this study to construct three distinct groups, namely: significant T wave negativity in isolated and combined derivations, aberration of the Q R S complex in all derivations, and significant T wave negativity associated with aberration of the Q R S complex in all derivations.

I have called attention to two pertinent facts regarding T wave negativity, that it never occurs alone in Derivation II nor in combined Derivations I and III, and that its occurrence alone in Derivation III has no prognostic significance, since it occurs often in normal hearts and may be an inconstant phenomenon.

In speaking of significant T wave negativity, I refer to the graphic arrangements, such as occurring (1) alone in Derivation I, (2) in combined Derivations I and II, (3) in combined Derivations II and III, and (4) in combined Derivations I, II, and III.

Patients who have had digitalis within six weeks of the time of examination have not been included, as T wave negativity may be the result of digitalis.

In this and subsequent studies the cases have been grouped according to clinical types. Control groups have been compiled for every group in this and subsequent studies. I wish clearly to define the control series to obviate any misunderstanding. In this study and in the following studies no control case is repeated. The control cases agree case for case in decade occurrence, clinical type, degree of decompensation and sex as far as possible. All the control patients had electrocardiographic study and the graphic criteria were absence of significant T wave negativity and absence of aberration of the Q R S complex in all derivations. Follow-up letters were not sent until both groups were compiled.

Study 1 comprises 449 cases and covers a period of five and one-half years. Patients are included who were examined at the Mayo Clinic up to Jan. 1, 1920. It was deemed unwise to include patients of the last two years.

The graphic arrangement of significant T wave negativity in order of frequency was (1) in combined Derivations II and III, 189 cases (42.1 per cent.); (2) alone in Derivation I, 146 cases (32.5 per cent.); (3) in combined Derivations I and II, sixty-three cases (14.0 per cent.), and (4) in combined Derivations I, II, and III, fifty-one cases (11.4 per cent.).

T WAVE NEGATIVITY ALONE IN DERIVATION I (146 CASES)

A. *Clinical Types of Heart Disease.*—The myocardial degeneration associated with hypertension occurred with greatest frequency in fifty-one cases (34.9 per cent.). In order of frequency the other clinical types of heart disease were angina pectoris, twenty-six cases (17.7 per cent.); chronic myocarditis and chronic endocardial valvular disease

with aortic regurgitation each twenty-one cases (14.3 per cent.); chronic endocardial valvular disease with mitral regurgitation, eleven cases (7.5 per cent.); myocardial degeneration associated with arteriosclerosis, five cases (3.4 per cent.); chronic endocardial valvular disease with aortic stenosis, four cases (2.7 per cent.); myocardial degeneration associated with exophthalmic goiter and adenoma with hyperthyroidism, each three cases (2 per cent.), and finally, chronic endocardial valvular disease with mitral regurgitation and stenosis, one case (0.7 per cent.).

The occurrence of T wave negativity and dominance in certain clinical types of cardiac involvement will be discussed elsewhere in this paper.

B. *Cardiac Mortality.*—The subgrouping of clinical types of heart disease in this study results in some groups which are too small for comprehensive and reliable statistical conclusions yet are presented not only for their interest but for the purpose of maintaining continuity in the presentation of data. It is interesting to note, however, that the mortality averages of the smaller groups in general are confirmed by the average of the complete group.

Information regarding 115 patients has been received (Table 1). Seventy-three (63.4 per cent.) have succumbed to heart disease in an average of eight and one-half months. Thirty-nine (33.9 per cent.) patients are living. Nine reported their conditions improved, eighteen unchanged, and twelve worse.

In striking contrast to these data are the results in the control series (Table 2). Ninty-three patients have been heard from. Twenty-six (26.8 per cent.) have died of heart disease in an average of two and four-tenths years; sixty (64.5 per cent.) are living; nineteen are improved; twenty-eight are unchanged, and thirteen are worse. The difference in mortality rate is so marked and the difference in average length of life so definite that further comment is hardly necessary.

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I AND II (SIXTY-THREE CASES)

A. *Clinical Types of Heart Disease.*—In this group, as in the foregoing, the myocardial degenerations associated with hypertension dominated—twenty-three cases (36.5 per cent.). The other clinical types of heart disease in order of frequency were chronic myocarditis, eleven cases (17.5 per cent.); angina pectoris, nine cases (14.3 per cent.); chronic endocardial valvular disease with aortic regurgitation, seven cases (11.1 per cent.); chronic endocardial valvular disease with mitral regurgitation, five cases (7.9 per cent.); myocardial degeneration associated with arteriosclerosis, four cases (6.3 per cent); myocardial degeneration associated with adenoma with hyperthyroidism, three cases (4.8 per cent.), and myocardial degeneration associated with exophthalmic goiter one case (1.6 per cent.).

B. *Cardiac Mortality.*—Forty-nine patients having T wave negativity in combined Derivations I and II of their electrocardiograms have been heard from and thirty-two (65.3 per cent.) have died of heart disease in an average of twelve and seven-tenths months. Seventeen (34.6 per cent.) are living. Four report their condition improved, eight unchanged, and five worse (Table 1).

In the control series of forty patients heard from, seven (17.5 per cent.) of the deaths occurred from heart disease and of the twenty-nine living patients (72.5 per cent.) thirteen are improved; eleven unchanged, and five worse (Table 2). Here, again, is observed a very striking difference in the mortality rates of the primary and the control series.

T WAVE NEGATIVITY IN COMBINED DERIVATIONS II AND III (189 CASES)

A. *Clinical Types of Heart Disease.*—T wave negativity in combined Derivations II and III occurred with greatest frequency in chronic myocarditis, forty-six cases (24.3 per cent.). The other clinical types of heart disease, in order of frequency, were myocardial degeneration associated with exophthalmic goiter, thirty-seven cases (19.6 per cent.); chronic endocardial valvular disease with mitral regurgitation, twenty-four cases (12.7 per cent.); myocardial degeneration associated with hypertension, twenty-two cases (11.6 per cent.); angina pectoris, sixteen cases (8.5 per cent.); chronic endocardial valvular disease with aortic regurgitation, eleven cases (5.8 per cent.); myocardial degeneration associated with adenoma with hyperthyroidism, ten cases (5.3 per cent.); chronic endocardial valvular disease with mitral stenosis, nine cases (4.8 per cent.); chronic endocardial valvular disease with mitral stenosis and regurgitation, five cases (2.6 per cent.); myocardial degeneration associated with arteriosclerosis and congenital heart disease each three cases (1.6 per cent.); syphilitic aortitis, two cases (1.1 per cent.), and chronic endocardial valvular disease with aortic stenosis, one case (0.5 per cent.).

B. *Cardiac Mortality.*—One hundred forty-nine patients in this group have been heard from, and forty-eight (32.2 per cent.) have succumbed to heart disease in an average of eleven months. Ninety-two (61.7 per cent.) are living and thirty-three report themselves improved, thirty-nine are unchanged, and twenty are worse (Table 1).

In the control series information regarding 110 patients has been received. Twenty-two (20 per cent.) have died of heart disease in an average of one and one-half years (Table 2).

T wave negativity in combined Derivations II and III is not attended by as high a cardiac mortality as are the other groups, an observation made in my previous study.

TABLE 1—CARDIAC MORTALITY WITH SIGNIFICANT T WAVE NEGATIVITY

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
T wave Negativity in Derivation I													
Hypertension	51	42	37	14	1	30	69.7	10.5	12	27.9	3	2	7
Chronic myocarditis	21	19	18	3	1	10	52.6	6.8	8	42.1	2	4	2
Arteriosclerosis	5	4	5	..	..	2	50.0	8.0	2	50.0	1	1	..
Angina pectoris	26	18	23	3	..	9	50.0	11.5	9	50.0	2	6	1
Exophthalmic goiter	2	2	..	2	..	2	100.0	4.5	..	....	....	..	..
Adenoma with hyperthyroidism	3	1	..	3	..	..	.....	....	1	100.0	...	1	..
Mitral regurgitation	11	6	6	5	..	4	66.6	10.0	2	33.3	...	2	..
Double mitral lesion	1	1	1	..	..	1	100.0	7.0	..	.....	....	..	..
Aortic regurgitation	21	18	19	2	1	12	66.6	10.0	5	27.7	1	2	2
Aortic stenosis	4	3	3	1	..	3	100.0	7.2	..	.....	....	..	..
Total	146	115	112	34	3	73	.....	....	39	.....	9	18	12
Average	...	...	...	..	..	..	63.4	8.5	..	33.9	...	..	..
T wave Negativity in Combined Derivations I and II													
Hypertension	22	20	14	9	..	16	80.0	10.9	4	20.0	1	2	1
Chronic myocarditis	11	9	7	4	..	2	22.2	2.5	7	77.7	1	4	2
Arteriosclerosis	4	3	3	1	..	3	100.0	5.5	..	.....	....	..	..
Angina pectoris	9	8	9	..	..	3	50.0	30.0	3	50.0	...	2	1
Exophthalmic goiter	1	1	...	1	..	..	.....	....	1	100.0	1	..	..
Adenoma with hyperthyroidism	3	...	1	2	..	..	.....	....	..	.....	....	..	..
Mitral regurgitation	5	4	5	..	..	4	100.0	9.0	..	.....	....	..	..
Aortic regurgitation	7	6	6	1	..	4	66.6	19.8	2	33.3	1	..	1
Total	63	49	45	18	..	32	.....	....	17	.....	4	8	5
Average	...	...	...	..	..	..	65.3	12.7	..	34.6	...	..	..
T wave Negativity in Combined Derivations II and III													
Hypertension	22	16	16	6	..	10	62.5	14.5	6	37.5	...	3	3
Chronic myocarditis	46	35	25	21	1	7	20.0	20.0	27	77.1	6	12	9
Arteriosclerosis	3	2	1	2	..	1	50.0	0.75	1	50.0	1	..	..
Angina pectoris	16	15	16	..	..	10	66.6	9.3	5	33.3	2	3	..
Exophthalmic goiter	37	28	7	30	3	3	10.7	16.6	22	78.5	17	3	2
Adenoma with hyperthyroidism	10	10	3	7	..	..	.....	....	10	100.0	6	1	3
Mitral regurgitation	24	19	8	16	2	11	57.8	9.8	6	31.5	1	3	2
Mitral stenosis	9	6	...	9	1	1	16.6	1.0	4	66.6	...	4	..
Double mitral lesion	5	5	1	4	1	3	60.0	16.6	1	20.0	...	1	..
Aortic regurgitation	11	9	9	2	1	2	22.2	?	6	66.6	...	6	..
Aortic stenosis	1	1	...	1	..	..	.....	....	1	100.0	...	..	1
Syphilitic aortitis	2	1	1	1	..	..	.....	....	1	100.0	...	1	..
Congenital heart disease	3	2	...	3	..	..	.....	....	2	100.0	...	2	..
Total	189	140	87	102	9	48	.....	....	92	.....	33	39	20
Average	...	...	...	..	..	..	32.2	11.0	..	61.7	...	..	..
T wave Negativity in Combined Derivations I, II, and III													
Hypertension	14	11	12	2	2	9	81.8	11.5	..	.....	....	..	..
Chronic myocarditis	8	6	4	4	..	2	33.3	24.0	4	66.6	...	2	2
Arteriosclerosis	1	1	1	..	..	1	100.0	?	..	.....	....	..	..
Angina pectoris	7	6	6	1	..	5	83.3	39.7	1	16.6	...	1	..
Exophthalmic goiter	2	2	2	..	..	.	.....	....	2	100.0	1	1	..
Adenoma with hyperthyroidism	2	1	...	2	..	..	.....	....	1	100.0	1	..	..
Mitral regurgitation	5	4	5	..	1	2	50.0	2.0	1	25.0	...	..	1
Aortic regurgitation	9	6	9	..	..	3	50.0	8.0	3	50.0	...	3	..
Double aortic lesion	2	2	1	1	..	2	100.0	9.5	..	.....	....	..	..
Congenital heart disease	1	1	1	..	..	1	100.0	1 day	..	.....	....	..	..
Total	51	40	41	10	3	25	.....	....	12	.....	2	7	3
Average	...	...	...	..	..	..	62.5	12.7	..	30.0	...	..	..
Grand total	449	353	285	164	15	178	.....	....	169	.....	48	72	40
Grand average	...	...	...	..	..	..	50.4	11.2	..	45.3	...	..	..

TABLE 2.—CONTROL SERIES

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
T wave Negativity in Derivation I													
Hypertension	51	35	21	30	2	11	31.4	14.3	22	62.8	4	11	7
Chronic myocarditis	21	14	14	7	..	4	28.0	31.2	10	71.0	5	3	2
Arteriosclerosis	5	4	5	..	..	..	.....	....	4	100.0	1	3	..
Angina pectoris	26	22	19	7	1	7	31.8	?	14	63.6	6	7	1
Exophthalmic goiter	3	3	...	3	..	..	.....	....	3	100.0	1	1	1
Adenoma with hyperthyroidism	3	1	...	3	..	..	.....	....	1	100.0	1	..	..
Mitral regurgitation	11	5	4	7	1	1	20.0	?	3	60.0	1	1	1
Double mitral lesion	1	1	1	..	1	..	.....	....	..	.....	...	..	..
Aortic regurgitation	21	6	15	6	1	2	33.3	?	3	50.0	...	2	1
Aortic stenosis	4	2	2	2	1	1	50.0	42.0	..	.....	...	..	..
Total	146	93	81	65	7	26	.....	....	60	.....	19	28	13
Average	...	...	...	..	..	..	36.8	28.8	..	64.5	...	..	..
T wave Negativity in Combined Derivations I and II													
Hypertension	23	13	13	10	3	2	15.3	4.5	8	61.5	4	2	2
Chronic myocarditis	11	8	6	5	..	2	25.0	6.5	6	75.0	1	5	..
Arteriosclerosis	4	4	3	1	..	1	25.0	36.0	3	75.0	3	..	..
Angina pectoris	9	5	8	1	1	..	.....	....	4	80.0	2	2	..
Exophthalmic goiter	1	..	...	1	..	..	.....	....	..	.....	...	..	..
Adenoma with hyperthyroidism	3	2	...	3	..	..	.....	....	2	100.0	...	1	1
Mitral regurgitation	5	4	5	..	..	1	25.0	7.0	3	75.0	1	1	1
Aortic regurgitation	7	4	5	2	..	1	25.0	?	3	75.0	2	..	1
Total	63	40	40	23	4	7	.....	....	29	.....	13	11	5
Average	...	...	...	..	..	..	17.5	10.8	..	72.5	...	..	..
T wave Negativity in Combined Derivations II and III													
Hypertension	22	11	15	7	..	4	36.3	9.7	7	63.6	4	..	3
Chronic myocarditis	46	29	27	19	2	5	17.2	20.4	22	75.8	9	10	3
Arteriosclerosis	3	1	3	..	1	..	.....	....	..	.....	...	..	..
Angina pectoris	16	10	12	4	..	2	20.0	24.0	8	80.0	...	8	..
Exophthalmic goiter	37	24	3	34	1	..	.....	....	22	95.8	16	5	2
Adenoma with hyperthyroidism	10	6	...	10	..	..	.....	....	6	100.0	3	3	..
Mitral regurgitation	24	14	12	12	2	7	50.0	15.8	5	35.7	1	2	2
Mitral stenosis	9	5	3	6	..	2	40.0	9.5	3	60.0	...	1	2
Double mitral lesion	5	2	3	2	..	1	50.0	22.0	1	50.0	1	..	..
Aortic regurgitation	11	4	8	3	..	1	25.0	36.0	3	75.0	1	2	..
Aortic stenosis	1	...	...	1	..	..	.....	....	..	.....	...	..	..
Syphilitic aortitis	2	1	1	1	..	..	.....	....	1	100.0	1	..	..
Congenital heart disease	3	3	...	3	..	..	.....	....	3	100.0	...	2	1
Total	189	110	87	102	6	22	.....	....	82	.....	36	33	13
Average	...	...	...	..	..	..	20.0	18.0	..	74.5	...	..	..
T wave Negativity in Combined Derivations I, II, and III													
Hypertension	14	10	5	9	..	1	10.0	42.0	9	90.0	3	6	..
Chronic myocarditis	8	6	4	4	1	3	50.0	13.0	2	33.3	1	1	..
Arteriosclerosis	1	1	1	..	..	..	.....	....	1	100.0	1	..	..
Angina pectoris	7	6	7	..	..	2	33.3	2.7	4	66.6	1	3	..
Exophthalmic goiter	2	1	2	..	..	..	.....	....	1	100.0	1	..	..
Adenoma with hyperthyroidism	2	2	...	2	..	..	.....	....	2	100.0	1	1	..
Mitral regurgitation	5	3	2	3	1	..	.....	....	2	66.6	1	1	..
Aortic regurgitation	9	7	6	3	1	2	28.5	?	4	57.1	1	3	..
Double aortic lesion	2	2	1	1	..	..	.....	....	2	100.0	...	1	1
Congenital heart disease	1	1	1	..	..	..	.....	....	1	100.0	...	1	..
Total	51	39	29	22	3	8	.....	....	28	.....	10	17	1
Average	...	...	...	..	..	..	20.5	19.2	..	71.7	...	..	..
Grand total	449	282	237	212	20	63	.....	....	199	.....	78	89	32
Grand average	...	...	...	..	..	..	22.3	19.2	..	70.5	...	..	..

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I, II, AND III
(FIFTY-ONE CASES)

A. *Clinical Types of Heart Disease.*—Myocardial degeneration associated with hypertension as in the first two groups dominates the clinical types of heart disease in T wave negativity in combined Derivations I, II and III. The other types in order of frequency were chronic endocardial valvular disease with aortic regurgitation, nine cases (17.6 per cent.); chronic myocarditis, eight cases (15.7 per cent.); angina pectoris, seven cases (13.7 per cent.); chronic endocardial valvular disease with mitral regurgitation, five cases (9.8 per cent.); myocardial degeneration associated with exophthalmic goiter, adenoma with hyperthyroidism and chornic endocardial valvular disease with aortic regurgitation, and stenosis, each two cases (3.9 per cent.); and finally, myocardial degeneration associated with arteriosclerosis and congenital heart disease, each one case (2 per cent).

B. *Cardiac Mortality.*—Forty patients have been traced and twenty-five (62.5 per cent.) have died of heart disease in an average of twelve and seven-tenths months. Twelve patients (30 per cent.) are living; two are improved, seven are unchanged, and three are worse.

In the control series thirty-nine patients have been heard from and eight (20.5 per cent.) have died of heart disease. Twenty-eight (71.7 per cent.) are living, ten are improved, seventeen are unchanged, and one patient is worse. This, again, is an instance of marked difference in cardiac mortality.

It is interesting to note how constant the cardiac mortality in the control series runs.

DISCUSSION

There can be no question with regard to the prognostic importance of significant T wave negativity. As I have said, the effect of digitalis must always be borne in mind and such cases of T wave negativity are inconstant and obviously do not fall in the category of the types under discussion. One is impressed with the constant association of significant T wave negativity and clinical evidence of serious cardiac disease.

I wish to call attention again to Table 1 and to the description of clinical types of heart disease which clearly depicts the dominance of conditions of the degenerative type. Foremost among them is the hypertension group, notorious for its attendant vascular degeneration. Chronic myocarditis extensively involving the musculature of the heart unquestionably affects the vascular elements of the organ. Likewise angina pectoris is constantly associated with vascular disease. Aortic regurgitation with its usual attendant aortitis has also a definite vascular basis.

Significant T wave negativity in all probability occurs in hearts involved by intrinsic vascular degeneration of the obliterative type. All our evidence at the present time suggests this theme and is based on clinical, pathologic, and experimental study. The high and early cardiac mortality rate attending significant T wave negativity implies a progressive disease process and further supports the foregoing concept.

Cardiac histopathology has failed miserably in attempting to explain and to clarify diseases of the myocardium. Conclusions have been based entirely on the presence or absence of actual tissue changes and no attention has been given to physiologic abnormalities. Only a few years ago a controversy arose regarding the causation of a certain electrocardiographic condition, and the arguments pro and con were based entirely on the presence or absence of gross and microscopic myocardial changes. One observer, by means of serial sections, demonstrated constant lesions in the heart muscle attending his bizarre graphs, and the other, by the same means, failed to find the tissue changes. Both sides of this controversy were seeking for the effect and not for the cause of the graphic anomalies, and we have many reasons to believe that a careful study of the vascular tree of the heart would have resulted in agreement. The presence of actual changes in the myocardium certainly is not necessarily a constant finding even though intrinsic vascular disease exists. With this concept in mind it is obvious that physiologic disturbances may often precede histopathologic changes.

SUMMARY

The cardiac mortality attending significant T wave negativity is high and is in sharp contrast to that in the control series. In order of importance the cardiac mortality is as follows:

T wave negativity in combined Derivations I and II, 65.3 per cent. in 12.7 months. Control series, 17.5 per cent. in 10.8 months.

T wave negativity alone in Derivation I, 63.4 per cent. in 8.5 months. Control series, 26.8 per cent. in 2.4 years.

T wave negativity in combined Derivations I, II and III, 62.5 per cent. in 12.7 months. Control series, 20.5 per cent. in 19.2 months.

T wave negativity in combined Derivations II and III, 32.2 per cent. in 11.0 months. Control series, 20.0 per cent. in 1.5 years.

Total of significant T wave negativity, 50.4 per cent. in 11.2 months. Total of control series, 22.3 per cent. in 19.2 months.

II. ABERRATION OF THE Q R S COMPLEX IN ALL DERIVATIONS OF THE ELECTROCARDIOGRAM *

Aberrations of the Q R S complex of the electrocardiogram involving all derivations have been the subject of considerable controversy. The variance of views has largely involved histopathologic issues. The

observer who has often noted this electrocardiographic abnormality and has correlated his graphic and clinical data is impressed with the gravity of the underlying cardiac disease.

In this group of cases, as in significant T wave negativity, an obliterative intrinisic vascular basis is strongly suggested.

Aberration of the Q R S complex of the electrocardiogram is characterized by notching of the apex, ascending or descending limb and in the complex of unaltered contour, a base width exceeding 0.10 second. The bizarre complex of high amplitude and diphasic in form is ascribed to bundle branch block while no definite localization is justifiable in the monophasic complex of lower amplitude.

TABLE 1.—Cardiac Mortality with Aberration of the Q R S Complex in All Derivations

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
Hypertension	17	10	9	8	..	8	80.0	18.3	2	20.0	...	2	..
Chronic myocarditis	29	21	19	10	1	9	42.8	6.6	11	52.4	2	5	.
Arteriosclerosis	15	13	12	3	..	10	76.9	23.6	3	23.0	1	2	..
Angina pectoris	10	9	7	3	..	6	66.6	23.1	3	33.3	...	3	..
Exophthalmic goiter	7	5	1	6	..	3	60.0	?	2	40.0	1	1	.
Adenoma with hyperthyroidism	9	8	...	9	1	3	37.5	7.7	4	50.0	2	1	1
Mitral regurgitation	10	6	8	2	1	5	83.3	12.5	..	.....	...	..	..
Double mitral lesion	3	3	1	2	..	1	33.3	15.0	2	66.6	...	1	1
Mitral stenosis	2	1	2	..	..	1	100.0	7.0	..	.....	...	..	..
Aortic regurgitation	10	5	9	1	..	5	100.0	?	..	.....	...	..	..
Total	112	81	68	44	3	51	.....	....	27	.....	6	15	6
Average	...	...	...	..	..	..	62.9	14.2	..	33.3	...	..	..

I have previously emphasized[1] the constant association of this graphic abnormality with serious and advanced heart disease and have shown the high and early cardiac mortality, occurring in this group. The cases presented were associated in many instances with significant T wave negativity, but those cases have not been included in this report.

This study comprises 112 cases covering a period of five and one-half years. The control series has been compiled based on the same conditions as in the foregoing study.

A. *Clinical Types of Heart Disease* (112 *Cases*).—Chronic myocarditis occurred with greatest frequency, twenty-nine cases (25.9 per cent.). The other clinical types of heart disease in order of frequency were the myocardial degeneration associated with hypertension, seventeen cases (15.2 per cent.); myocardial degeneration associated with arterio-

1. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (April) 1919.

sclerosis, fifteen cases (13.4 per cent.); angina pectoris, chronic endocardial valvular disease with mitral regurgitation, and aortic regurgitation, each ten cases (8.9 per cent.); myocardial degeneration associated with adenoma with hyperthyroidism, nine cases (8 per cent.); exophthalmic goiter, seven cases (6.3 per cent.); chronic endocardial valvular disease with mitral regurgitation and stenosis, three cases (2.7 per cent.), and finally, chronic endocardial valvular disease with mitral stenosis, two cases (1.8 per cent.). It is quite evident that degenerative diseases also dominate this group.

B. *Cardiac Mortality.*—Information has been obtained regarding eighty-one patients and fifty-one (62.9 per cent.) have died of heart

TABLE 2.—CONTROL SERIES

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
Hypertension	17	9	8	9	1	1	11.1	3.0	7	77.7	3	4	..
Chronic myocarditis	29	14	20	9	3	4	28.5	17.5	7	50.0	2	5	..
Arteriosclerosis	15	9	14	1	..	2	22.2	33.0	7	77.7	1	6	..
Angina pectoris	10	6	6	4	1	2	33.3	5.0	3	50.0	1	2	..
Exophthalmic goiter	7	5	1	6	..	..	.....	....	5	100.0	2	3	..
Adenoma with hyperthyroidism	9	5	1	8	..	..	.....	....	5	100.0	3	2	..
Mitral regurgitation	10	6	7	3	..	3	50.0	3.5	3	50.0	...	3	..
Double mitral lesion	3	2	2	1	1	..	.....	....	1	50.0	1	..	..
Mitral stenosis	2	2	1	1	..	..	.....	....	2	100.0	1	..	1
Aortic regurgitation	10	7	8	2	..	2	28.5	20.0	5	71.4	...	3	2
Total	112	65	68	44	6	14	.....	....	45	.....	14	28	3
Average	...	...	...	..	..	..	21.5	12.7	..	69.2	...	..	..

disease in an average of fourteen and two-tenths months. Twenty-seven (33.3 per cent.) patients are living and of these, six are improved, fifteen are unchanged, and six are worse (Table 1).

In striking relief to these averages are the results of the control series. Sixty-five patients have been heard from, and only fourteen (21.5 per cent.) have succumbed to heart disease in an average of thirteen and seven-tenths months. Forty-five (69.2 per cent.) are alive; fourteen are improved, twenty-eight are unchanged, and three are worse (Table 2).

DISCUSSION

The great difference in cardiac mortality between cases exhibiting aberration of the Q R S complex in all derivations of the electrocardiogram and identical clinical types of cardiac disease in which this graphic abnormality does not exist is convincing. The only justifiable criticism that is apparent to me is the reliability of the control series. In Study I,

I have defined the criteria for all the control groups and have shown that in all respects except an accurate sex agreement the controls were identical case for case exclusive, of course, of the electrocardiographic changes under discussion.

The early and high mortality is indicative of a progressive process and, as previously stated, favors the concept of obliterative intrinsic vascular disease.

SUMMARY

The cardiac mortality attending aberration of the Q R S complex in all derivations of the electrocardiogram practically trebles that of the control series.

Aberrant Q R S complexes in all derivations, cardiac mortality, 62.9 per cent. in 14.2 months.

Control series, cardiac mortality, 21.3 per cent. in 13.7 months.

NOTE.—No attempt has been made to record a complete bibliography dealing with aberration of the Q R S complex as the pros and cons of the arguments regarding this abnormality are already recorded in most of the previous publications dealing with this subject.

III. SIGNIFICANT T WAVE NEGATIVITY AND ABERRATION OF THE Q R S COMPLEX IN ALL DERIVATIONS OF THE ELECTROCARDIOGRAM

The foregoing studies have emphasized the prognostic importance of significant T wave negativity and of aberration of the Q R S complex occurring in all derivations of the electrocardiogram. This study is of cases in which these graphic abnormalities occurred together. With the preceding statistics in mind it is reasonable to anticipate a greater cardiac mortality in this study. Patients exhibiting both electrocardiographic abnormalities generally have more marked subjective and objective evidence of cardiac damage than those in whom these graphic changes occur separately.

One hundred and thirty-five cases are included in this study which covers a period of five and one-half years.

The control groups are based on the criteria of those in the preceding groups.

T WAVE NEGATIVITY ALONE IN DERIVATION I AND ABERRATION OF THE Q R S COMPLEX IN ALL DERIVATIONS (NINETY CASES)

A. *Clinical Types of Heart Disease.*—The myocardial degeneration associated with hypertension occurred with greatest frequency, thirty-five cases (38.9 per cent.). The other types in order of frequency were chronic myocarditis, twenty-two cases (24.4 per cent.); chronic endocardial valvular disease with aortic regurgitation, eight cases (8.9

per cent.); angina pectoris, seven cases (7.8 per cent.); myocardial degeneration associated with arteriosclerosis and chronic endocardial valvular disease with mitral regurgitation, each five cases (5.6 per cent.); adenoma with hyperthyroidism, four cases (4.4 per cent.) and exophthalmic goiter, one case (1.1 per cent.).

B. *Cardiac Mortality.*—Information regarding seventy-three patients has been received and sixty-three (86.3 per cent.) have died of heart disease in an average of eight and four-tenths months following examination. Seven patients (9.5 per cent.) are alive and of these two are improved, two are unchanged, and three are worse (Table 1).

The control group sharply contrasts this mortality. Sixty patients have been heard from and eighteen (30 per cent.) have succumbed to heart disease in an average of twenty-one and four-tenths months following examination. Thirty-eight (63.3 per cent.) are living and eleven report their condition improved, twenty-two unchanged, and five worse (Table 2).

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I AND II AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS (TWENTY-THREE CASES)

A. *Clinical Types of Heart Disease.*—Myocardial degeneration associated with hypertension again is an outstanding condition, twelve cases (52.2 per cent.). The other clinical types in order of frequency are chronic myocarditis and chronic endocardial valvular disease with aortic regurgitation each, three cases (13 per cent.); angina pectoris and chronic endocardial valvular disease with mitral regurgitation each, two cases (8.7 per cent.), and aortic aneurysm, one case (4.3 per cent.).

B. *Cardiac Mortality.*—Twenty patients have been traced and all but one have died of heart disease (95 per cent.) in an average of eight and one-half months following examination. The surviving patient (5 per cent.) is worse (Table 1).

In the control group facts regarding sixteen patients have been received. Three (18.7 per cent.) have died of heart disease in an average of six and seven-tenths months following examination. Of the nine living patients (56.2 per cent.) six are unchanged and three are worse (Table 2).

T WAVE NEGATIVITY IN COMBINED DERIVATIONS II AND III AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS (SEVENTEEN CASES)

A. *Clinical Types of Heart Disease.*—Chronic myocarditis occurred with greatest frequency, five cases (29.4 per cent.). The other types

TABLE 1.—Cardiac Mortality with Significant T Wave Negativity and Aberration of the Q R S Complex in All Derivations

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
T wave Negativity in Derivation I and Aberration of the Q R S Complex in all Derivations:													
Hypertension	35	28	22	13	2	23	82.1	15.4	3	10.7	...	1	2
Chronic myocarditis	22	16	17	5	..	15	93.7	9.0	1	6.2	...	1	..
Arteriosclerosis	5	4	4	1	..	3	75.0	0.9	1	25.0	...	..	1
Angina pectoris	7	5	6	1	..	5	100.0	2.4	..	.....	...	..	..
Exophthalmic goiter	1	1	...	1	..	..	.....	.....	1	100.0	1	..	..
Adenoma with hyperthyroidism	4	4	1	3	1	3	75.0	18.0	..	.....	...	..	..
Mitral regurgitation	5	4	3	2	..	3	75.0	?	1	25.0	1	..	..
Double mitral lesion	3	2	2	1	..	3	100.0	3.2	..	.....	...	..	..
Aortic regurgitation	8	8	8	..	..	8	100.0	9 8	..	.....	...	..	..
Total	90	73	63	27	3	63	.....	....	7	.....	2	2	3
Average	...	...	...	..	..	..	86.3	8.4	..	9.5	...	..	..
T wave Negativity in Combined Derivations I and II and Aberration of the Q R S Complex in all Derivations:													
Hypertension	12	11	10	2	..	11	100.0	12.8	..	.....	...	..	..
Chronic myocarditis	3	2	2	1	..	2	100 0	1.7	..	.....	...	..	..
Angina pectoris	2	2	2	..	..	2	100.0	5.0	..	.....	...	..	..
Mitral regurgitation	2	1	1	1	..	1	100.0	11.0	..	.....	...	..	..
Aortic regurgitation	3	3	3	..	..	3	100.0	12.0	..	.....	...	..	..
Aortic aneurysm	1	1	1	..	..	..	.....	....	1	100.0	...	..	1
Total	23	20	19	4	..	19	.....	....	1	.....	...	..	1
Average	...	...	...	..	..	..	95.0	8.5	..	5.0	...	..	..
T wave Negativity in Combined Derivations II and III and Aberration of the Q R S Complex in all Derivations:													
Hypertension	3	2	2	1	..	2	100.0	?	..	.....	...	..	..
Chronic myocarditis	5	5	4	1	..	2	40.0	13.0	3	60.0	1	2	..
Arteriosclerosis	1	1	1	..	..	1	100.0	20.0	..	.....	...	..	..
Angina pectoris	3	3	3	..	..	2	66.6	37.2	1	33.3	...	..	..
Mitral regurgitation	2	2	1	1	..	2	100.0	20.5	..	.....	...	..	..
Double mitral lesion	1	1	1	..	..	1	100.0	3.0	..	.....	...	..	..
Aortic regurgitation	2	1	2	..	..	1	100.0	51.6	..	.....	...	..	..
Total	17	15	14	3	..	11	.....	....	4	.....	1	2	1
Average	...	...	...	..	..	..	73.3	22.8	..	26.6	...	..	..
T wave Negativity in Combined Derivations I, II, and III and Aberration of the Q R S Complex in all Derivations:													
Hypertension	2	2	2	..	..	2	100.0	15.5	..	.....	...	..	..
Chronic myocarditis	1	1	1	..	..	1	100.0	18.0	..	.....	...	..	..
Angina pectoris	1	1	1	..	..	1	100.0	9.0	..	.....	...	..	..
Aortic regurgitation	1	1	1	..	..	1	100.0	3.0	..	.....	...	..	..
Total	5	5	5	..	..	5	.....	....	..	.....	...	..	..
Average	...	...	...	..	..	..	100.0	11.1	..	.....	...	..	..
Grand total	135	113	101	34	3	98	.....	....	12	.....	3	4	5
Grand average	...	...	...	..	..	..	86.7	12.7	..	10.0	...	..	..

TABLE 2.—CONTROL SERIES

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
T wave Negativity in Derivation I and Aberration of the Q R S Complex in all Derivations:													
Hypertension	35	26	17	18	3	8	30.7	28.5	15	57.6	3	11	1
Chronic myocarditis	22	14	17	5	1	4	28.5	18.0	9	64.2	3	5	1
Arteriosclerosis	6	2	3	2	..	..	.....	....	2	100.0	...	1	1
Angina pectoris	7	5	7	..	..	2	40.0	12.0	3	60.0	1	2	..
Exophthalmic goiter	1	1	1	..	..	..	.....	....	1	100.0	...	..	1
Adenoma with hyperthyroidism	4	4	1	3	..	..	.....	....	4	100.0	3	1	..
Mitral regurgitation	5	2	4	1	..	1	50.0	12.0	1	50.0	...	1	..
Double mitral lesion	3	1	2	1	..	1	100.0	10 0	..	.....	...	..	..
Aortic regurgitation	8	5	6	2	..	2	40.0	48.0	3	60.0	1	1	1
Total	90	60	58	32	4	18	.....	....	38	.....	11	22	5
Average	...	...	...	..	..	..	30.0	21.4	..	63.3	...	..	..
T wave Negativity in Combined Derivation I and II and Aberration of the Q R S Complex in all Derivations:													
Hypertension	12	8	8	4	3	3	37.5	6 7	2	25.0	...	1	1
Chronic myocarditis	3	3	3	..	1	..	.....	....	2	66.6	...	1	1
Angina pectoris	2	2	2	..	..	..	.....	....	2	100.0	...	2	..
Mitral regurgitation	2	1	...	2	..	..	.....	....	1	100 0	...	..	1
Aortic regurgitation	3	2	2	1	..	..	.....	....	2	100.0	...	2	..
Aortic aneurysm	1	...	...	1	..	..	.....	....	..	.....	...	..	..
Total	23	16	15	8	4	3	.....	....	9	.....	...	6	3
Average	...	...	...	..	..	..	18.7	6.7	..	56.2	...	..	..
T wave Negativity in Combined Derivation II and III and Aberration of the Q R S Complex in all Derivations:													
Hypertension	3	3	2	1	..	2	66.6	7.0	1	33.3	...	1	..
Chronic myocarditis	5	4	4	1	..	1	25.0	2.0	3	75.6	...	2	1
Arteriosclerosis	1	1	...	1	..	..	.....	....	1	100 0	...	..	1
Angina pectoris	3	3	3	..	1	1	33.3	18.0	1	33.3	1	..	..
Mitral regurgitation	2	1	1	1	1	..	.....	....	..	.....	...	..	..
Double mitral lesion	1	1	...	1	..	..	.....	....	1	.....	1	..	..
Aortic regurgitation	2	2	2	..	..	..	.....	....	2	100.0	1	1	..
Total	17	15	12	5	2	4	.....	....	9	.....	3	4	2
Average	...	...	...	..	..	..	26.6	13.5	..	60.0	...	..	..
T wave Negativity in Combined Derivations I, II, and III and Aberration of the Q R S Complex in all Derivations:													
Hypertension	2	2	2	..	2	..	.....	....	..	.....	...	..	..
Chronic myocarditis	1	1	1	..	..	..	.....	....	1	100 0	...	1	..
Angina pectoris	1	1	1	..	..	..	.....	....	1	100.0	...	1	..
Aortic regurgitation	1	...	...	1	..	..	.....	....	..	.....	...	..	..
Total	5	4	4	1	2	..	.....	....	2	.....	...	2	..
Average	...	...	...	..	..	..	.....	....	..	50.0	...	..	..
Grand total	135	95	89	46	12	25	.....	....	58	.....	14	34	10
Grand average	...	...	...	..	..	..	26.3	13.9	..	61.0	...	..	..

were myocardial degeneration associated with hypertension and angina pectoris, each three cases (17.6 per cent.); chronic endocardial valvular disease with mitral regurgitation and with aortic regurgitation, each two cases (11.8 per cent.), and myocardial degeneration associated with arteriosclerosis and chronic endocardial valvular disease with mitral regurgitation and stenosis, each one case (5.9 per cent.).

B. *Cardiac Mortality.*—Fifteen patients have been heard from and

TABLE 3.—SUMMARY OF THE MORTALITY STATISTICS IN GROUPS 1, 2 AND 3

Clinical Classification	Total Number	Patients Heard From	Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
				Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
T wave negativity in Derivation I	146	115	3	73	65.4	8.5	39	33.9	9	18	12
T wave negativity in combined Derivations I and II	63	49	..	32	65.3	12.7	17	34.6	4	8	5
T wave negativity in combined Derivations II and III	189	149	9	48	32.2	11.0	92	61.7	33	39	20
T wave negativity in combined Derivations I, II, and III	51	40	3	25	62.5	12.7	12	30.0	2	7	3
Total	449	353	15	178	....	....	160	....	58	72	40
Average	...	...	...	...	50.4	11.2	...	45.3	..	..	..
Aberration of the Q R S complex in all derivations	112	81	3	51	62.9	14.2	27	33.3	6	15	6
T wave negativity in Derivation I and aberration of the Q R S complex in all derivations	90	73	3	63	86.3	8.4	7	9.5	2	2	3
T wave negativity in combined Derivations I and II and aberration of the Q R S complex in all derivations	23	19	..	19	95.0	8.5	1	5.0	..	..	1
T wave negativity in combined Derivations II and III and aberration of the Q R S complex in all derivations	17	15	..	11	73.3	22.8	4	26.6	1	2	1
T wave negativity in combined Derivations I, II, and III and aberration of the Q R S complex in all derivations	5	5	.	5	100.0	11.1	...	....	..	..	..
Total	135	113	3	98	....	....	12	....	3	4	5
Average	...	...	...	...	86.7	12.7	...	10.6	..	..	..

eleven (73.3 per cent.) have died of heart disease in one and nine-tenths years following examination. Four patients (26.6 per cent.) are living and one is improved, two are unchanged, and one is worse (Table 1).

Fifteen patients in the control group have been heard from and four (26.6 per cent.) have died of heart disease in an average of thirteen and one-half months following examination. Nine patients are living (60 per cent.), three are improved, four are unchanged, and two are worse (Table 2).

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I, II, AND III AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS (FIVE CASES)

This group is too small to be of statistical value but is presented to maintain continuity of data.

A. *Clinical Types of Heart Disease.*—Myocardial degeneration associated with hypertension occurred in two cases (40 per cent.) and chronic

TABLE 4.—SUMMARY OF THE MORTALITY STATISTICS OF THE CONTROL SERIES IN GROUPS 1, 2 AND 3

Clinical Classification	Total Number	Patients Heard From	Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
				Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
Control Series to											
T wave negativity in Derivation I	146	93	7	26	20.8	23.8	60	64.5	19	28	13
T wave negativity in combined Derivations I and II	63	40	4	7	17.5	10.8	29	72.5	13	11	5
T wave negativity in combined Derivations II and III	189	110	6	22	20.0	18.0	82	74.5	36	33	13
T wave negativity in combined Derivations I, II, and III	51	39	2	8	20.5	19.2	28	71.7	10	17	1
Total	449	282	20	63	....	....	199	....	78	89	3
Average	...	...	...	...	22.3	19.2	...	70.5	..	..	..
Aberration of the QRS complex in all derivations	112	65	6	14	21.5	13.7	45	69.2	14	28	3
T wave negativity in Derivation I and aberration of the QRS complex in all derivations	90	60	4	18	30.0	21.4	38	63.3	11	22	5
T wave negativity in combined Derivations I and II and aberration of the QRS complex in all derivations	23	16	4	3	18.7	6.7	9	56.2	0	6	3
T wave negativity in combined Derivations II and III and aberration of the QRS complex in all derivations	17	15	2	4	26.6	13.5	9	60.0	3	4	2
T wave negativity in combined Derivations I, II, and III and aberration of the QRS complex in all derivations	5	4	2	..	....	....	2	50.0	..	2	..
Total	135	95	12	25	....	....	58	....	14	34	10
Average	...	...	...	...	26.3	13.9	...	61.0	..	..	..

myocarditis, angina pectoris, and chronic endocardial valvular disease with aortic regurgitation, each one case (20 per cent.).

B. *Cardiac Mortality.*—All patients have been traced and all have died of heart disease (100 per cent.), in an average of eleven and one-tenth months following examination (Table 1).

Four patients in the control series have been heard from and no cardiac deaths are recorded. Two patients are alive and report their condition unchanged (Table 2).

The high and early cardiac mortality attending significant T wave negativity associated with aberration of the Q R S complex in all derivations is apparent. The association of these electrocardiographic abnormalities is an index of marked myocardial involvement and is attended by the greatest mortality in the three studies.

SUMMARY

The cardiac mortality attending significant T wave negativity and aberration of the Q R S complex in all derivations in order of importance as revealed in this study was:

T wave negativity in combined Derivations I, II and III and aberration of the Q R S complex in all derivations, 86.7 per cent. in 12.7 months. Control series, 0.

T wave negativity in combined Derivations I and II and aberration of the Q R S complex in all derivations, 95.0 per cent. in 8.5 months. Control series, 18.7 per cent. in 6.7 months.

T wave negativity alone in Derivation I and aberration of the Q R S complex in all derivations, 86.3 per cent. in 8.4 months. Control series, 30.0 per cent. in 21.4 months.

T wave negativity in combined Derivations II and III and aberration of the Q R S complex in all derivations, 73.3 per cent. in 22.8 months. Control series, 26.6 per cent. in 13.5 months.

Total of group, 86.7 per cent. in 12.7 months. Control series, 26.3 per cent. in 13.9 months.

Tables 3 and 4 have been constructed to summarize the mortality statistics of the three groups. From the standpoint of prognosis the electrocardiographic abnormalities rank in order of importance as follows: (1) significant T wave negativity associated with aberration of the Q R S complex in all derivations of the electrocardiogram (group cardiac mortality 86.7 per cent. in twelve and seven-tenths months); (2) aberration of the Q R S complex in all derivations of the electrocardiogram (group cardiac mortality 62.9 per cent. in fourteen and two-tenths months), and (3) significant T wave negativity (group cardiac mortality 50.4 per cent. in eleven and two-tenths months).

These statistics, I hope, will help to allay the scepticism of some cardiologists regarding the significance of the electrocardiographic disorders under discussion. The recognition of these graphic changes alone, I believe, justifies the use of the electrocardiograph as a most valuable and important clinical adjunct.

CLINICAL STUDIES OF QUINIDIN

II. ALTERATIONS IN THE CARDIAC MECHANISM AFTER ADMINISTRATION OF QUINIDIN TO PATIENTS WITH AURICULAR FIBRILLATION WITH CONSIDERATION OF CERTAIN TOXIC EFFECTS OF THE DRUG *

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During the past four years, sufficient evidence has been accumulated to indicate that in a certain number of patients suffering from fibrillation of the auricles (about 50 per cent.), oral administration of quinidin sulphate serves to restore the normal cardiac rhythm. The circumstances which determine the issue are not yet altogether clear. A summary of the earlier literature, together with a preliminary report dealing with the treatment of four cases in the Hospital of the Rockefeller Institute, has already appeared.[1]

The results of experiments done in this Hospital to determine the pharmacologic action of this drug have likewise been reported.[2] It is the purpose of the present communication to record in detail the alterations in the mechanism of the heart's action which have been observed in the first eleven patients to whom quinidin has been administered.[3] A more detailed report of the experimental studies will appear shortly. A discussion of the clinical aspects of quinidin therapy is reserved for a subsequent paper in which a larger material will be considered.[4]

MATERIAL AND METHOD

Five hundred and seven electrocardiograms, taken of eleven patients, have been measured and analyzed. The cases represent an unselected material. They have been under observation prior to treatment for periods ranging from one month to one and a half years, and are known to have been fibrillating for at least these periods of time.

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* From the Hospital of the Rockefeller Institute for Medical Research.
* Presented in abstract before the New York Academy of Medicine, Nov. 17, 1921

1. Levy, R. L.: Restoration of the Normal Cardiac Mechanism in Auricular Fibrillation by Quinidin; Preliminary Report, J. A. M. A. **76**:1289 (May 7) 1921.

2. Cohn, A. E., and Levy, R. L.: Experimental Studies of the Pharmacology of Quinidin, Proc. Soc. Exper. Biol. & M. **18**:283, 1921. Experiments with Quinidin on Conduction and on the Refractory Period in the Dog's Heart. Proc. Soc. Exper. Biol. & M. **19**:174, 1922.

3. A preliminary account of this study was published in the Proc. Soc. Exper. Biol. & M. **19**:88, 1921.

4. In this paper will be considered the symptoms attendant on administration of the drug, the duration of its action, the effects of altered rhythm on vital capacity and heart size as determined teleroentgenographically, the relationship between digitalis and quinidin therapy, etc.

After a preliminary dose of from 0.2 to 0.4 gm. quinidin to test for the presence of an idosyncrasy to members of the cinchona group, 0.4 gm. of the drug has been given by mouth, in gelatin capsules, either three times daily or every two hours, until the establishment of normal rhythm or the appearance of untoward symptoms indicated cessation of therapy. No more than 2 gm. quinidin was administered in twenty-four hours, though treatment has been continued daily for as long as ten days.

Electrocardiograms were taken in some instances as often as every five minutes during the time when a change of rhythm was anticipated. Usually curves were made at one or two hour intervals on the days on which the drug was given and at least once daily throughout the entire period of observation. The usual three limb leads were employed. Records made in this fashion do not always permit of accurate measurement of auricular rate when the auricles are fibrillating. References to rate, therefore, unless otherwise specified, are to be taken as indicating the number of ventricular beats per minute.

RESULTS

The results of this electrocardiographic study are of interest in illustrating the great variety of alterations in the mechanism of the heart's action which may be induced by quinidin. They have, furthermore, a significance for clinical medicine in so far as they indicate the manner in which the transition from fibrillation to normal rhythm may be expected to occur. But of paramount importance is the significance attached to various toxic effects which have been observed, as evidenced by the occurrence of rhythms usually associated with poisoning of the heart muscle. It is particularly desirable that those concerned with the care and treatment of patients with heart disease should be familiar with the signs and dangers of quinidin intoxication.

For the purpose of discussion, the eleven cases naturally fall into two groups: (1) three patients, in whom, on different occasions, the normal mechanism was restored nine times, and who, in all, received twelve courses of quinidin; (2) eight patients, in whom restoration of the normal mechanism was not accomplished and who received, in all, eleven courses of quinidin. Detailed case records are appended.

CASES IN WHICH THE NORMAL RHYTHM WAS RESTORED

Sequence of Events.—In order to learn in what sequence the various changes in cardiac mechanism occurred, detailed analyses of all electrocardiograms were chronologically charted. A summary of the findings is given in Table 1.

The first effect noted was usually acceleration of ventricular rate. On the other hand when the rate was initially very rapid (Case 1,

Courses 2, 3 and 4), the drug caused a reduction in the number of ventricular contractions. Alterations in rate occurred in from one to three hours after beginning treatment. Tachycardia was followed at times by the appearance of premature beats, arising more commonly in the right, but occasionally in the left ventricle. The ectopic ventricular contractions were frequently transitory (Cases 1 and 2), but in one case (Case 3), they were the precursors of paroxysms of ventricular tachycardia, to which particular reference will be made later. If electrocardiograms were taken at sufficiently frequent intervals, the transitional mechanisms in the common order of their appearance were: coarser fibrillation, that is to say, waves in the electrocardiogram having a higher voltage and denoting retardation of auricular rate;[5] impure auricular flutter;[6] auricular flutter, and finally, normal rhythm (Fig. 4). This sequence was not invariably exhibited in all its phases and it is possible that one or more of the intermediate mechanisms may be omitted.

Transition.—In one patient the transition from auricular flutter to the normal rhythm was photographed in the second lead (Fig. 5). The abruptness of the change is remarkable. The first twelve interauricular intervals in the curve range from 0.2180 to 0.2580 second (Table 2) with maximum variation of 0.04 second. The corresponding phases of successive cycles are strikingly uniform in contour. The maximum variation in interventricular intervals is 0.0240 second.[7] There follows a period of altering auricular activity, denoted by the next seven P waves, which exhibit increasingly greater deviations from the usual form. The interauricular intervals are, on the whole, longer than in

5. Drury, A. N., and Iliescu, C. C.: The Restoration of the Normal Cardiac Mechanism in Cases of Auricular Fibrillation by Means of Quinidin Sulphate, Brit. M. J. **7**:511 (Oct. 1) 1921. These authors, by use of direct chest leads, have secured records in which accurate counts of auricular rate were possible and have noted progressive retardation after quinidin.

6. By impure auricular flutter is meant a mechanism in which auricular (P) waves are present, but in which they are somewhat irregularly spaced and of varying contour, in contradistinction to the regularity of interauricular intervals and constancy of form of corresponding P waves in pure flutter. It is to be regarded as intermediate between auricular fibrillation and flutter.

7. Lewis, T., in speaking of the lengths of auricular cycles in auricular flutter, states that "the maximal variation of the cycles in the same curves is usually less, probably considerably less than 0.01 second; probably it may amount to, but does not materially exceed, 0.02 second on occasion. It seems advisable that the term auricular flutter should be confined to disorders, be they clinical or experimental, in which comparable variations in the lengths of auricular cycles are found not to be exceeded." Heart **7**:127, 1920. These statements are based on measurements of the curves of seven cases of flutter, in which interventricular, not interauricular intervals were determined. In one of these cases the maximal variation in interventricular intervals was 0.0265 second. A discussion of the validity of Lewis' criteria is not within the scope of this paper. There seems no reason to doubt that the curve shown in Figure 5 is a record of auricular flutter.

TABLE 1.—Summary of Cases in Which the Normal Mechanism Was Restored

Case and Hosp. Nos.	Clinical Diagnosis	Quinidin, Gm.	Duration of Admin., Days	Original Mechanism	Effect on				Mechanisms After Quinidin										Remarks
					Rate	P-R Sec.	T	QRS	Coarse Fib.	Impure Flutter	Fib. + Imp. Flutter	Flutter	Normal Rhythm	VPCR	VPCL	APC	Vent. Tachy.	S. A. Block	Aur. Tachy.	
1 3968	Syphilis; chronic myocarditis	4.6	6	Aur. Fib.;* VPL; VPCL	+ (1)†	0.13-0.15	+ (5)	.....	.....	+ (3)	.....	.....	+ (4)	+ (2)	.....	+ (6)	.....	.....	.....	Patient partly digitalized prior to quinidin administration; APC appeared after onset of normal rhythm
		1.2	1	Aur. Fib.; VPL	— (2)	0.12-0.14	+ (3)	+ (5)	.....	+ (4)	.....	+ (6)	+ (7)	+ (1)	.....	+ (8)	.....	.....	.....	Patient not digitalized; ventricular rate 185 before quinidin administration; APC again appeared after onset of normal rhythm; 6 days after prolongation of QRS was noted, it returned to normal duration
		0.4	1	Aur. Fib.; VPL	— (1)	0.12-0.13	+ (3)	.....	.....	.....	.....	.....	+ (2)	.....	.....	+ (4)				
		0.4	1	Aur. Fib.; VPL	— (2)	0.12-0.14	+ (4)	.....	.....	.....	.....	+ (1)	+ (3)	.....	.....	+ (5)				
		1.2	1	Normal rhythm; VPL, APC, VPCR	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	APC and VPCR disappeared after quinidin
2 4330	Chronic endocarditis; mitral stenosis and insufficiency	1.6	2	Aur. Fib.; VPR	+ (1)	0.16	+ (5)	.....	.....	.....	.....	+ (2)	+ (4)	.....	+ (3)	+ (6)	.....	.....	.....	T wave changed and APC appeared after onset of normal rhythm; impure flutter intervened between normal rhythm and reversion to fibrillation
		0.8	1	Aur. Fib.; VPR	— (1)	0.14-0.16	+ (3)	.....	.....	.....	.....	.....	+ (2)	.....	.....	+ (4)	.....	.....	.....	APC inconstant
		0.4	1	Aur. Fib.; impure flutter; flutter	— (3)	0.16-0.17	+ (5)	.....	.....	+ (1)	.....	+ (2)	+ (4)							
3 4118	Chronic endocarditis; mitral stenosis and insufficiency	1.2	1	Aur. Fib.	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	No significant effect
		8.4	7	Aur. Fib.	+ (1)	0.21-0.24	+ (8)	.....	.....	+ (6)	+ (4)	.....	+ (7)	+ (7	+ (5)	+ (11)	+ (3)	+ (9)	+ (10)	T wave change transient; sino-auricular block observed once after onset of normal rhythm; one paroxysm of auricular tachycardia after onset of normal rhythm
		6.4	5	Aur. Fib	— (2)	0.21	+ (7)	.....	.....	+ (5)	+ (3)	.....	+ (6)	+ (1)	+ (4)	.....	.....	.....	.....	Normal rhythm maintained for less than 24 hours
		1.6	1	Aur. Fib.	+ (1)	.....	.....	.....	.....	.....	+ (2)	.....	.....	+ (4)	+ (5)	.....	+ (3)			

* Key to abbreviations used in Tables 1 and 2:
Aur. Fib.: Auricular fibrillation.
VPCR: Ventricular premature contractions, right.
VPCL: Ventricular premature contractions, left.
VPR: Ventricular preponderance, right
VPL: Ventricular preponderance, left.
APC: Auricular premature contractions.
Vent. Tachy.: Ventricular tachycardia.
Aur. Tachy.: Auricular tachycardia.
S-A Block: Sino-auricular block.

† The numbers in the various columns denote the chronologic sequence of the changes observed. Under rate, + = acceleration; — = retardation.

the group immediately preceding, and range from 0.2280 to 0.2860 second, with maximum variation of 0.0580 second. There is coincidently gradual widening of the interventricular periods. Then comes a relatively long asystole of both auricles and ventricles and this is followed by prompt resumption of the sinus rhythm.

A consideration of the manner in which the transition occurs is of some interest in relation to the theory that a circus excitation is the nature of the disturbed mechanism at the basis of fibrillation and flutter of the auricles. According to this concept, first clearly defined by A. G. Mayer, working with the umbrella of the jelly fish, developed and demonstrated in heart muscle by Garrey and by Mines, and more recently elaborated and applied to human physiology by Lewis, cessa-

TABLE 2.—MEASUREMENT OF ELECTROCARDIOGRAM (LEAD II) SHOWING TRANSITION FROM AURICULAR FLUTTER TO NORMAL RHYTHM *

Cardiac Mechanism	Interauricular Intervals, Second	Interventricular Intervals, Second	P-R Time, Second
Auricular flutter	0.2324		
	0.2510	0.4520	
	0.2200		
	0.2300	0.4760	
	0.2180		
	0.2288	0.4608	
	0.2200		
	0.2230	0.4606	
	0.2212		
	0.2210	0.4530	
	0 2580		
	0.2210	0.4558	
Altering auricular activity	0.2455		
	0.2362	0.4936	
	0.2280		
	0.2860	0.5760	
	0.2610		
	0.2430	0.6310	
Transition	1.0889	1.0849	
Normal rhythm	0.7720	0.7752	0.1696
	0.8200	0.8256	0.1632
	0.8450	0.8456	0.1640
	0.8594	0.8610	0.1620

* Measurements were made with the use of a projection apparatus.

tion of auricular fibrillation or flutter may, on theoretic grounds, be induced in three ways: (1) by lengthening the path of the excitation wave in the auricle; (2) by accelerating the rate of conduction of the impulse through the auricular muscle; (3) by lengthening the refractory period of this muscle. It is clear from the electrocardiogram shown in Figure 5, that immediately before and during the transition the excitation wave is traversing a different path from that travelled during the preceding period of flutter; for the P waves alter in form. They are, moreover, irregularly and more widely spaced. To which of the three conceivable causes just mentioned this change may be ascribed, it is not possible definitely to establish. It is known, however, that in the dog's heart, quinidin retards the rate of conduction

of the impulse through the muscle of the auricle and prolongs the refractory period.[2-8] It furthermore raises the threshold of excitability of the auricle, so that a faradic current adequate to induce fibrillation prior to the injection of quinidin does not suffice to cause the arrhythmia after the drug has been given.[2] It is probable that the resultant of these effects determines whether cessation of fibrillation takes place. Slowing of the conduction rate may be regarded as exerting an unfavorable or negative effect in arresting the circus movement, whereas the raised threshold of excitability and more particularly, lengthening of the refractory period, exercise a favorable or positive effect in promoting this result. The decreased rate of the flutter waves in this instance at all events indicates that probably a longer path, perhaps at a slower rate, was traversed by the excitation wave. The alteration in path may have been necessitated by an increase in the refractory period.

After the resumption of normal rhythm, the auricular waves, though distinct, showed at times decided variations both in contour and voltage. Evidence of such change in the P waves (Fig. 5) in Cycles 14 and 39 is striking. There is apparently still a tendency for the impulse to be initiated at a point other than at the sinus node or to traverse an unusual and sinuous path in its course through the auricle.

Ectopic Beats; Auricular Tachycardia; Sino-Auricular Block.—Ectopic auricular contractions were observed in all three cases at times after the normal mechanism was resumed. Their occurrence points to the persistent presence of a point of origin away from the sinus node, and probably within the musculature of the auricle. Additional evidence strengthening the belief that there is disturbance in both initiation and propagation of the impulse through the auricle in individuals suffering from atrial fibrillation is afforded by Case 3, in which, during the brief period in which normal rhythm was maintained, sino-auricular block and paroxysms of ectopic auricular tachycardia occurred (Fig 6).

When auricular premature beats became numerous, these, as well as ectopic ventricular contractions, could be abolished by the further administration of quinidin (Case 1, fifth course; Fig. 3). It is to be noted that the ventricular premature beats disappeared earlier than those arising in the auricle.[9]

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8. Lewis, T.; Drury, A. N.; Iliescu, C. C., and Wedd, A. M.: Observations Relating to the Action of Quinidin on the Dog's Heart, with Special Reference to Its Action on Clinical Fibrillation of the Auricles, Heart **9**:55, 1921.

9. We have since had occasion to test the effect of quinidin in patients showing no disturbance in rhythm other than ectopic beats arising either in auricles or ventricles. In certain of these individuals, the undisturbed normal mechanism can be restored and, if desired, maintained by proper quinidin dosage.

Rate.—On the day on which normal rhythm was established, the ventricular rate usually ranged from 80 to 90 and on the following day from 60 to 70, subsequently remaining at or about this level during the period in which the sequential rhythm prevailed. When the transition from the normal rhythm to fibrillation or flutter took place, there was correspondingly a gradual acceleration of rate, a level eventually being reached in the course of twenty-four hours at which the ventricles then continued to beat with relatively slight variations.

A-V Conduction.—Conduction through the auriculoventricular bundle when the sinus rhythm was present was within normal limits in two cases, as indicated by the P-R time. In the third case the P-R interval was prolonged (0.24 sec.); but it is not possible to say whether this was a drug effect or was due to interference with the passage of the impulse from other causes.

Intra-Ventricular Conduction.—In one individual (Case 1, second course), there was definite evidence that quinidin caused interference with the spread of the excitation wave through the ventricles (partial intraventricular block) (Fig. 1). The Q R S interval rose from 0.10 sec. before quinidin administration to 0.13 sec. after the drug had been given, and did not return to its former value for five days. There was no coincident prolongation of A-V conduction.

Alteration in Ventricular Complex.—In the series of curves just described (Fig.1) is seen an example of change in the contour and voltage of the ventricular complex after quinidin administration. This is exhibited particularly in the R and S waves and in the altered form and position of the notching. Similar changes were observed in one other case. There is, presumably, some change in the path of the impulse through the ventricles.

T Wave.—The T wave was distinctly affected by quinidin, in that it tended to reverse its direction and change its form after the normal rhythm was established.[1] Though slight variations in this portion of the electrocardiogram were among the early effects of quinidin medication, the more striking changes occurred after the sinus rhythm had prevailed for twenty-four hours and were best seen in Lead III (Fig. 2). When the fibrillatory mechanism was resumed, the T wave usually returned to its original direction and form either at once or after a short interval. It is of interest to note that in one instance, however, (Case 2, first course), the T wave change preceded the alteration in cardiac mechanism. On the last day of normal rhythm the T wave in Lead III changed from upright to inverted. On the following morning, auricular fibrillation was again recorded, the T wave remaining as on the previous day. It is, therefore, clear that, although change in the form of the T wave and change in rhythm often occur synchro-

nously, they are not necessarily interdependent. In dogs in which quinidin was injected similar alterations in the T wave were noted.[8] These observations are recorded without any attempt at interpretation, since the significance of change in this portion of the electrocardiogram is by no means clear.

Influence of Digitalis.—Digitalization prior to quinidinization was not essential for success in restoring the normal mechanism. For in the same individual (Case 1), the normal rhythm was on one occasion restored after digitalis administration, with ventricular rate ranging from 90 to 100 (first course), and at another time, after no digitalis was given, when the ventricles were beating at the rate of 180 per minute (second course). A number of observations bearing on this point have been made and will be discussed more fully at another time.

Effect of Atropin.—Intravenous injection of atropin sulphate (from 1.0 to 1.5 mgm.) in these patients at a time when fibrillation was present and again when the normal rhythm prevailed, resulted in the usual increase in ventricular rate, but in no noteworthy alteration in the cardiac mechanism or in the form of the electrocardiogram.

CASES IN WHICH RESTORATION OF THE NORMAL MECHANISM WAS NOT ACCOMPLISHED

In this group of eight patients, evidences of the undesirable action of quinidin were more frequently observed (Table 3).

Tachycardia.—As in the cases in which it was possible to establish normal rhythm, tachycardia was commonly the first effect noted and was often sufficiently troublesome to cause complaint. Having once been initiated, it was rarely prolonged beyond four or five hours after the drug was discontinued. In one patient (Case 10, first course), in whom simple tachycardia was induced by quinidin, definite signs and symptoms of heart failure ensued. There was palpitation, dyspnea, epigastric distress, large tender liver, accumulation of invisible edema, as evidenced by gain in weight and oliguria and a striking rise in venous pressure from 10.8 to 20.2 cm. of water.[10] A graphic account of these findings is given in Figure 9. A course of digitalis therapy was followed by prompt disappearance of symptoms and signs of decompensation.

Coarse Fibrillation; Impure Flutter; Flutter.—Coarsening of fibrillatory waves, indicating retardation of auricular rate, was noted on five occasions. It was at times among the earliest detected changes in the electrocardiogram, but in other instances was seen as a later

10. Observations of venous pressure were made by the method of Hooker: Am. J. Physiol. **35**:73, 1914.

TABLE 3.—Summary of Cases in Which Restoration of the Normal Rhythm Was Not Accomplished

Case and Hosp. Nos.	Clinical Diagnosis	Quinidin, Gm.	Duration of Admin. Days	Original Mechanism	Effect on				Mechanisms After Quinidin									Remarks
					Rate	P-R	T	QRS	Coarse Fib.	Impure Flutter	Fib. + Imp. Flutter	Flutter	Normal Rhythm	VPCR	VPCL	APC	Vent. Tachy	
4 3083	Chronic endocarditis; mitral stenosis and insufficiency; aortic insufficiency	4.8	5	Aur. Fib.; VPR	+ (1)	.....	.....	.....	.....	.....	.....	.....	.....	+ (2)				
5 4274	Chronic endocarditis; mitral stenosis and insufficiency; aortic insufficiency	4.0	7	Aur. Fib.; VPR; VPCL	+ (1)	.....	.....	.....	+ (4)	.....	+ (5)	+ (6)	.....	+ (2)	+ (3)			
6 4127	Chronic endocarditis; mitral stenosis and insufficiency	3.6	5	Aur. Fib.; VPR; VPCR (occasional)	+ (1)	.....	.....	.....	.....	.....	.....	.....	.....	+ (2)	+ (4)	.....	+ (3)	Patient digitalized before beginning quinidin therapy; VPCR increased in number, at times resulting in coupled rhythm
7 4227	Chronic myocarditis	3.2	5	Aur. Fib.; VPL	+ (3)	.....	.....	.....	.....	.....	+ (6)	+ (5)	.....	+ (1)	+ (3)	.....	+ (4)	After digitalis, fibrillatory mechanism returned
8 4345	Chronic endocarditis; mitral stenosis and insufficiency	6.2	8	Aur. Fib	+ (1)	.....	+ (3)	.....	+ (6)	+ (4)	.....	.....	.....	+ (5)	+ (2)			
9 4306	Chronic endocarditis; mitral stenosis and insufficiency	2.4	3	Aur. Fib.	+ (1)	.....	+ (3)	.....	+ (4)	+ (5)	+ (6)	.....	.....	.....	+ (2)			
10 4349	Chronic endocarditis; mitral stenosis and insufficiency; aortic insufficiency	3.0	4	Aur. Fib.	+ (1)	.....	+ (3)	.....	.....	.....	.....	.....	.....	+ (2)	.....	.....	.....	Patient digitalized prior to quinidin administration
		1.6	3	Aur. Fib.	+ (3)	.....	+ (4)	.....	+ (1)	.....	.....	.....	.....	+ (2)	.....	.....	.....	Patient again digitalized before beginning quinidin
		4.0	5	Aur. Fib.	+ (1)	.....	+ (2)	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Quinidin and digitalis combined
11 4267	Chronic myocarditis	8.8	10	Aur. Fib.; VPL	+ (2)	.....	.....	.....	+ (3)	.....	.....	.....	.....	.....	+ (1)	.....	+ (4)	Patient digitalized before beginning quinidin therapy

effect. The mechanism by which slowing is produced is not precisely to be ascertained. It is known, however, that one of the pharmacologic actions of quinidin is to depress conductivity in the auricle, and it is conceivable, and altogether likely, that slowed auricular rate is an exhibition of this effect. When still greater depression of conduction has been produced, impure flutter occurs. This was observed on three occasions in combination with periods of fibrillation and twice as the dominant rhythm. In two patients (Cases 5 and 7) impure flutter was followed by flutter, but larger dosage was not effective in restoring the normal rhythm. In Case 5, the flutter was of short duration, lasting but twenty minutes, after which a mixed rhythm with periods of fibrillation and impure flutter was recorded. In Case 7, however, flutter persisted for three days and was followed, after administration of digitalis, by reversion to the fibrillatory rhythm.

These observations serve to demonstrate the close interrelationship between fibrillation, impure flutter and flutter, and lend support to the concept that they are all dependent upon the same basic disturbance, namely, a circus contraction in the auricle. In these respects, Lewis' experimental data [11] are confirmed for the clinic.

Ventricular Premature Beats.—Of the greatest significance to the clinician are those arrhythmias which indicate irritation of the ventricular muscle. Reference has already been made, in discussing the first group of cases, to the occurrence of ectopic ventricular premature beats, which arose more often in the right, but occasionally in the left ventricle. These were observed in all of the eight cases in the series now under discussion. In some instances they were transitory, disappearing spontaneously or after more of the drug was given. They assume particular importance in those individuals in whom occasional ventricular premature beats are not present prior to the beginning of treatment. They may occur as isolated extrasystoles; or, in such fashion as to cause coupled rhythm, like that seen in the early stages of digitalis poisoning (Case 6, first course; Fig. 7).

Paroxysms of Ventricular Tachycardia.—If more quinidin is given, however, ventricular premature beats may occur in rapid succession in a manner to result in paroxysms of ectopic ventricular tachycardia (Cases 3, 6, 7 and 11, Figs. 6 and 8), or as a continuous sequence of extrasystoles arising in an ectopic focus in the ventricle (Case 7, Fig. 8). Case 7 is of particular interest in this connection, in that ventricular tachycardia occurred at first during the fibrillatory period, then at a time when auricular flutter with 3:1 block was present and subsequently, with slower auricular rate and 2:1 block. The

11. Lewis, T.: Observations upon Flutter and Fibrillation. Part IV. Impure Flutter; Theory of Circus Movement, Heart **7**:293, 1920.

paroxysms in the three cases in which this mechanism was seen were fortunately of short duration, lasting always less than twenty hours and sometimes disappearing in the course of three hours after the last dose of quinidin was given.

Ventricular tachycardia assumes a real significance if it is borne in mind that in dogs injected with digitalis or strophanthin this irregularity is not infrequently the precursor of ventricular fibrillation and death. Dogs which have received quinidin occasionally, though rarely, die with this arrhythmia.[2] Several sudden and unexplained deaths are reported by careful observers following quinidin administration in patients in whom, at necropsy, dilatation of the heart but no evidence of pulmonary or other embolism was found. It is quite possible that in these patients ventricular fibrillation was the cause of death. Unfortunately, the cardiac mechanism shortly before and at the time of death has not been recorded.

In certain individuals, then, quinidin is a highly toxic substance for heart muscle, even in doses ordinarily regarded as safe in clinical therapeutics. Until further details of its action are known, it is wise to insist that patients receiving this drug should remain in bed, preferably in a hospital, under close observation by nurse and physician. Where possible, therapy should be controlled by graphic records. Physicians who prescribe quinidin should do so with the realization that in proper hands it possesses great therapeutic virtue, whereas unintelligently given, it may cause disastrous effects and fall into undeserved disrepute.

SUMMARY

1. An electrocardiographic study has been made of eleven patients with auricular fibrillation who received quinidin sulphate by mouth. In three, to whom quinidin was given on twelve occasions, the normal rhythm was restored nine times. In eight, to whom the drug was given on eleven occasions, restoration of the normal rhythm was not accomplished.

2. In the cases in which normal rhythm was established, the first effect noted was usually acceleration of ventricular rate; next in order came ectopic ventricular beats. The transitional mechanisms in the common order of appearance were: coarser fibrillation, denoting retardation of auricular rate, impure flutter, flutter and normal rhythm.

3. The transition from flutter to normal rhythm has been photographed in the second lead and has been described.

4. The occurrence of variations in the form of P waves, ectopic auricular contractions, auricular tachycardia and sino-auricular block after resumption of the sinus rhythm, is adduced as evidence that there is, even at this time, a tendency for the impulse to be initiated at a point other than at the sinus node and to traverse an unusual path in its course through the auricle.

5. Both auricular and ventricular premature beats could, on occasion, be abolished by further exhibition of the drug.

6. The effects on rate, A-V conduction, intraventricular conduction and on the T wave have been discussed.

7. Reference has been made to the influence of digitalis on the issue of quinidin administration and to the effect of atropin after establishment of the sinus rhythm.

8. In the cases in which restoration of the normal mechanism was not accomplished, evidences of the undesirable action of quinidin were more frequently observed. Tachycardia was troublesome and in one instance was followed by signs and symptoms of heart failure.

9. The close interrelationship of fibrillation, impure flutter and flutter was evident in that rapid change from one of these mechanisms to the other was frequently seen. This observation lends support to the concept that they are all dependent on the same basic disturbance, namely, a circus contraction in the auricles.

10. Ectopic ventricular beats were seen after quinidin in all of the eight cases under discussion. These occurred at times in such fashion as to cause coupled rhythm.

11. After the continued administration of quinidin, paroxysms of ectopic ventricular tachycardia sometimes ensued. This arrhythmia is significant for the clinican; for in dogs injected with digitalis or strophanthin it is not infrequently the precursor of ventricular fibrillation and death. In the three cases in which this mechanism was seen, the paroxysms were fortunately of short duration.

12. In certain patients, quinidin is a toxic substance for heart muscle, even in doses ordinarily regarded as safe for clinical use. Carefully administered, the drug possesses great therapeutic virtue, whereas unintelligently given, it may be expected to cause undesirable effects.

APPENDIX

REPORT OF CASES

CASES IN WHICH THE NORMAL MECHANISM WAS RESTORED

CASE 1.—Hosp. No. 3968. Male, aged 55. Diagnosis: Syphilis; chronic myocarditis. Known duration of fibrillation, one and a half years; duration of cardiac symptoms, two years.

This patient received quinidin sulphate on five different occasions, four times to restore the normal rhythm, the fifth time in an attempt to abolish auricular and ventricular premature beats at a time when the sinus rhythm prevailed.

First Course.—March 10 to 15: 4.5 gm. were given in six days. The patient had been taking 0.1 gm. digitalis (digitan) daily prior to quinidin administration. The original mechanism, as recorded electrocardiographically, was fine auricular fibrillation. There was left ventricular preponderance and an occasional left ventricular premature beat.

First Day: 0.2 gm. at 3 and 6 p. m. There was no evident effect.

Second Day: 0.2 gm. at 7, 9, 11 a. m. and 1 and 3 p. m. At 10:50 a. m., after 0.8 gm., the ventricular rate rose from 110 to 142 and right ventricular

premature contractions appeared; these were transient and were not again observed during this course of treatment. By 4 p. m. the rate had again fallen to 95.

Third and Fourth Days: No quinidin given.

Fifth Day: 0.4 gm. at 12 noon, 4 and 8 p. m. Again there was acceleration of rate, which at 6 p. m. was 130.

Sixth Day: At 6 a. m., the ventricular rate was 140, with but 114 beats palpable at the wrist. 0.4 gm. at 8 and 10 a. m., 12 noon, 2:15 and 4 p. m. At 2:50 p. m., after 1.6 gm., there was impure flutter with ventricular rate of 115. This was followed, after another 0.4 gm., by restoration of the normal mechanism with rate of 80. The sinus rhythm was recorded one hour and fifty-five minutes after the onset of flutter. On the following day the T wave in Lead III, which

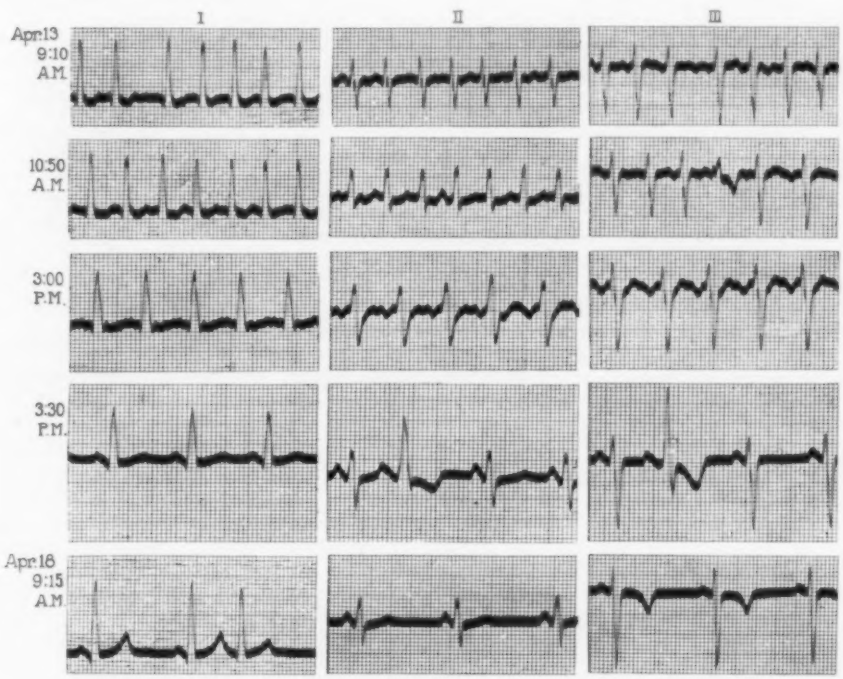

Fig. 1.—Case 1. Hosp. No. 3968. April 13: Quinidin sulphate, 0.4 gm., at 10:30 a. m., 12 noon, and 2:30 p. m.

9:10 a. m., control. Auricular fibrillation; ventricular rate, 185; Q R S = 0.10 sec.

10:50 a. m., after 0.4 gm. Auricular fibrillation; ventricular rate, 185; right ventricular premature contraction (Lead III).

3:00 p. m., thirty minutes after 1.2 gm. Auricular flutter; auricular rate, 280; ventricular rate, 140. Q R S = 0.13 sec.

3:30 p. m., one hour after 1.2 gm. Normal rhythm; ventricular rate, 95; P-R = 0.13 sec. Q R S = 0.13 sec.

April 18, five days later. 9:15 a. m. Normal rhythm; auricular premature contractions; ventricular rate, 60; P-R = 0.13 sec.; Q R S = 0.10 sec.

had been upright, became inverted and auricular premature beats were present. The latter disappeared spontaneously after being present for four days. The P-R (conduction) time during the period of normal rhythm ranged from 0.13 to 0.16 second. The sinus rhythm prevailed for twenty-three days. On the twenty-fourth day fine auricular fibrillation with ventricular rate of from 120 to 135 suddenly reappeared. In the course of three days the T wave in all three leads assumed the opposite direction from that previously recorded. There were occasional left ventricular premature beats. On the twenty-fifth day the ventricular rate rose to 184 and remained at this level until quinidin was again administered five days later.

Second Course.—April 13: Three doses of 0.4 gm. each were given at two hour intervals. After 0.4 gm., right ventricular premature contractions appeared, but were transitory. After 0.8 gm. there was gradual fall in rate from 180 to

Case 1. Hosp. No. 3968

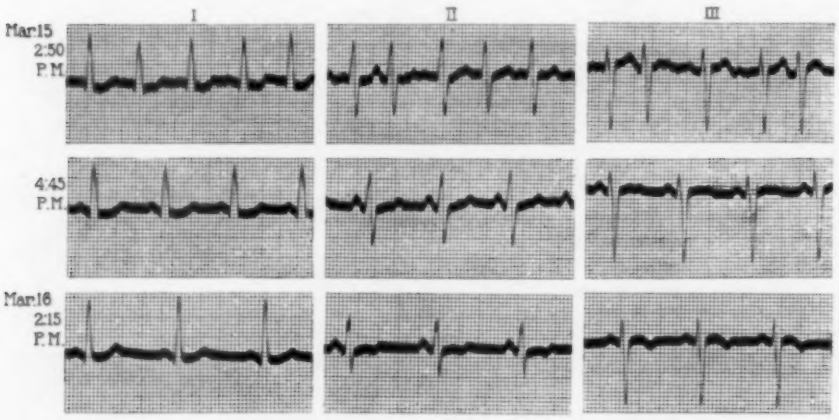

Fig. 2.—Case 1. Hosp. No. 3968. March 15: Quinidin sulphate, 0.4 gm., at 8 and 10 a. m., 12 noon, 2:15 and 4 p. m.

2:50 p. m., after 1.6 gm. Auricular fibrillation; ventricular rate 115; T wave $= \mp + +$.

4:45 p. m., forty-five minutes after 2 gm. Normal rhythm; ventricular rate 80; P-R = 0.15 sec.; T wave $= + + +$.

March 16, twenty-one hours later. 2:15 p. m. Normal rhythm; ventricular rate 69; P-R = 0.14 sec.; T wave $= + \mp -$.

140. The T wave in Lead I changed from inverted to upright. Three hours after beginning treatment and one hour after the second dose, there was impure flutter with ventricular rate of 145. The Q R S interval was 0.10 second. Impure flutter persisted for forty minutes after which 2:1 flutter was recorded. The Q R S interval was now from 0.12 to 0.13 second. After forty-five minutes of flutter, normal rhythm with rate of 95 was established. The T wave in Lead III changed at once from upright to inverted. Auricular and right ventricular premature beats were present, the latter disappearing in the course of a few hours. The Q R S interval still ranged from 0.12 to 0.13 second. Next day the rate was 69 and was maintained at about 70, until fibrillation reappeared twenty-one days after onset of normal rhythm. Q R S group remained wider than normal, i. e., more than 0.10 second, for six days, then resumed its former value of 0.10 second. On the twenty-first day of normal rhythm fibrillation

with ventricular rate of 120 set in. Next day there was further acceleration of rate, from 170 to 180, and the T wave in Lead III changed from inverted to upright.

Third Course.—May 6: 0.4 gm. sufficed to restore normal rhythm on this occasion, the ventricular rate falling rapidly from 185 to 94, and on the following day to 72. The T wave in Lead III again changed from upright to inverted and auricular premature beats appeared. Normal rhythm was present for only four days; then for a day fibrillation supervened, for a few hours there was spontaneous resumption of normal rhythm and then again reversion to fibrillation with ventricular rate of 180. After the onset of fibrillation the T wave in Lead III again became upright. While the sinus rhythm prevailed, P-R (conduction) time was from 0.12 to 0.13 second.

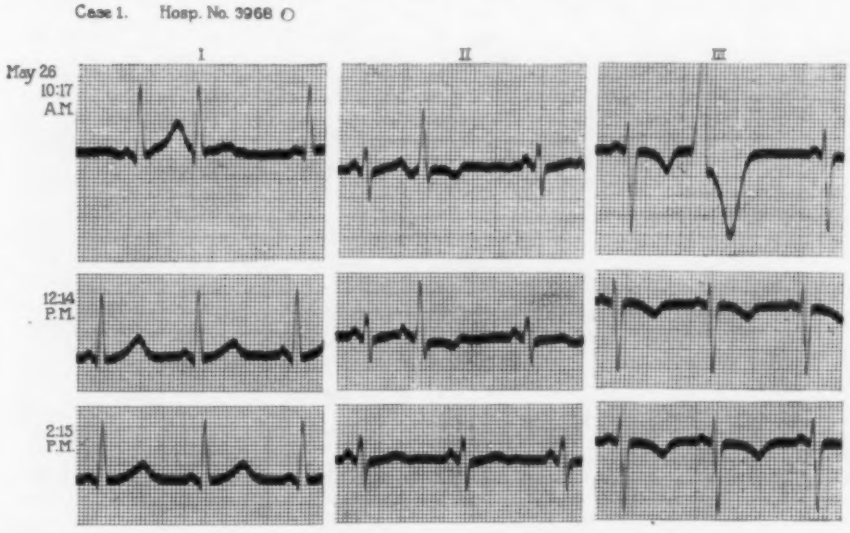

Fig. 3.—Case 1. Hosp. No. 3968. May 26: Quinidin sulphate, 0.4 gm., at 8 and 11 a. m., and 1 p. m.

10:17 a. m., after 0.4 gm. Normal rhythm; auricular and right ventricular premature contractions; rate 75; P-R = 0.13 sec.

12:14 p. m., after 0.8 gm. Normal rhythm; auricular premature contractions; rate 66; P-R = 0.14 sec.

2:15 p. m., after 1.2 gm. Normal rhythm; rate 61; P-R = 0.12 sec.

Fourth Course.—May 18: After seven days of fibrillatory mechanism, 0.4 gm. was again given, and 2:1 flutter ensued forty minutes after quinidin was taken with no demonstrated intermediate mechanism. When flutter first appeared, the ventricular rate was 180 but fell in the course of thirty-five minutes to 145. One hour and two minutes after the onset of flutter there was a normal rhythm at the rate of 108. There were occasional auricular premature beats. The T wave in Lead III changed from upright to inverted. At the end of four hours the ventricular rate had fallen to 75. P-R (conduction) time was from 0.12 to 0.14 second. Three days after the establishment of normal rhythm auricular flutter reappeared but the fibrillatory mechanism was not resumed. On the following day one dose of 0.4 gm. sufficed once more to restore the normal mechanism though occasional auricular premature beats were present.

Fifth Course.—May 26: In the course of four days many premature contractions, both of auricular and right ventricular origin, were present. These were sufficiently numerous to cause complaint; 1.2 gm., given in three doses of 0.4 gm. each, at three hour intervals sufficed entirely to abolish the ectopic contractions. The normal rhythm has now been maintained in this patient for more than eleven months. He has been taking 0.4 gm. quinidin every second day, and three doses of 0.4 gm. each on one day every two weeks. At times premature beats of auricular origin have been present, but the larger dosage has usually served to restore the undisturbed normal mechanism.

CASE 2.—Hosp. No. 4330. Male, aged 26. Diagnosis: Chronic endocarditis (rheumatic); mitral stenosis and insufficiency. Known duration of fibrillation, one month; duration of cardiac symptoms, eight years.

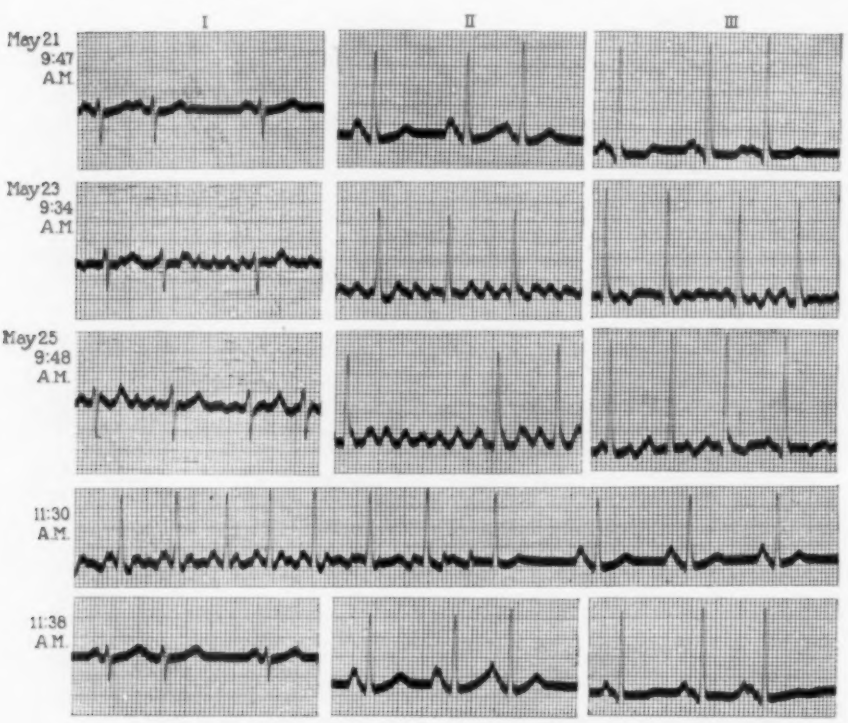

Fig. 4.—Case 2. Hosp. No. 4330. Normal rhythm had prevailed for eighteen days after a previous course of quinidin. May 21: 9:47 a. m. Normal rhythm still present; rate 80; P-R = 0.15 sec.

May 23: 9:34 a. m. Auricular fibrillation and impure flutter; ventricular rate 92.

May 25: 9:48 a. m., control. Impure flutter and flutter; ventricular rate 90.

10:05 a. m., quinidin sulphate, 0.4 gm.

11:30 a. m., eighty-five minutes after 0.4 gm. Lead II. Transition from auricular flutter, with ventricular rate of 122 and auricular rate of 244, to normal rhythm, with ventricular rate of 72; P-R = 0.16 sec.

11:38 a. m. Normal rhythm; ventricular rate 86; P-R = 0.16 sec.

This patient received three courses of quinidin, each time with restoration of normal rhythm. He was kept in bed in the hospital for one month without medication before beginning quinidin administration. The original mechanism was coarse auricular fibrillation; there was right ventricular preponderance. Ventricular rate prior to treatment ranged from 100 to 110.

First Course.—March 17 and 18: 1.6 gm. given in two days.

First Day: 0.2 gm., at 11:30 a. m. and 1:30 p. m. The first effect noted was an increase in the rate of the ventricles to 125, even after this small preliminary dose. At 4:30 p. m., three hours after the second dose, there was auricular flutter with 3:1 block.

Second Day: 0.4 gm. at 7, 9 and 11 a. m. At 9:30 a. m., thirty minutes after the second dose, the rate was 140, and the mechanism auricular flutter with 3:1 block. There were a few left ventricular premature beats. One hour and five minutes after 1.2 gm. had been given, normal rhythm was established with a rate of 95. Premature beats were no longer present. The T wave in Lead III, which, prior to treatment, had been inverted, became upright in the course of two hours. There was a progressive fall in rate and at the end of five hours the ventricles were beating 73 times per minute. P-R (conduction) time was from 0.16 to 0.17 second. There were occasional auricular premature beats. The normal rhythm was maintained for thirteen days. It is of interest to note that on the last day of normal rhythm the T wave in Lead III again changed from upright to inverted, and the following morning auricular fibrillation was recorded once again, the T wave remaining as on the previous day. Ventricular rate was 110. Two days later there was impure flutter with rate of 130, followed by coarse fibrillation with rate ranging from 110 to 115.

Second Course.—April 7: On the eighth day after reversion to fibrillation, 0.4 gm. was given at 7 and 9 a. m. The normal rhythm was again promptly reestablished at 9:30, the intermediate mechanisms, if such were present, not being recorded. The ventricular rate was 85. The T wave in Lead III again changed from inverted to upright, and auricular premature beats were present. These were observed to disappear and reappear at times. P-R (conduction) time was from 0.14 to 0.16 second. On this occasion the normal rhythm persisted for twenty-three days, the ventricular rate ranging from 66 to 80. On the twenty-third day there was again auricular fibrillation with a ventricular rate of 120 and the T wave in Lead III became inverted. Four days later the normal rhythm was resumed without medication, and persisted for twenty days, the P-R (conduction) time being from 0.15 to 0.16 second and the T wave in Lead III being upright. Again there were occasional auricular premature beats. On the twentieth day there was a mixture of auricular flutter and fibrillation, with ventricular rate of 92 and an inverted T wave in Lead III. On the following day there were seen in the same curve both impure flutter and auricular fibrillation, and on the day after this flutter, impure flutter and auricular fibrillation.

Third Course.—May 25: 0.4 gm. was given at 10:05 a. m. At 11 o'clock there was impure flutter, and at 11:30, one hour and twenty-five minutes after quinidin had been given, the transition from auricular flutter to the normal mechanism was recorded in Lead II. There were occasional auricular premature beats. T_3 was again upright. There was a fall in ventricular rate from 122 during the period of flutter, to 72 after the sinus rhythm was restored. The P-R (conduction) time ranged from 0.16 to 0.17 second.

The patient was discharged from the hospital three days later with a normal rhythm, but did not report for observation as directed. He returned for examination four months later showing the fibrillatory mechanism with a ventricular rate of 96. Three doses, of 0.4 gm. each, again restored the normal mechanism, and this was maintained for three months with the intermittent quinidin medication given on a plan similar in its essentals to that outlined for Case 1.

Case 3.—Male, aged 55. Diagnosis: Chronic endocarditis (rheumatic); mitral stenosis and insufficiency. Known duration of fibrillation, fifteen months; duration of cardiac symptoms, six years.

Case 2. Hosp. No. 4330

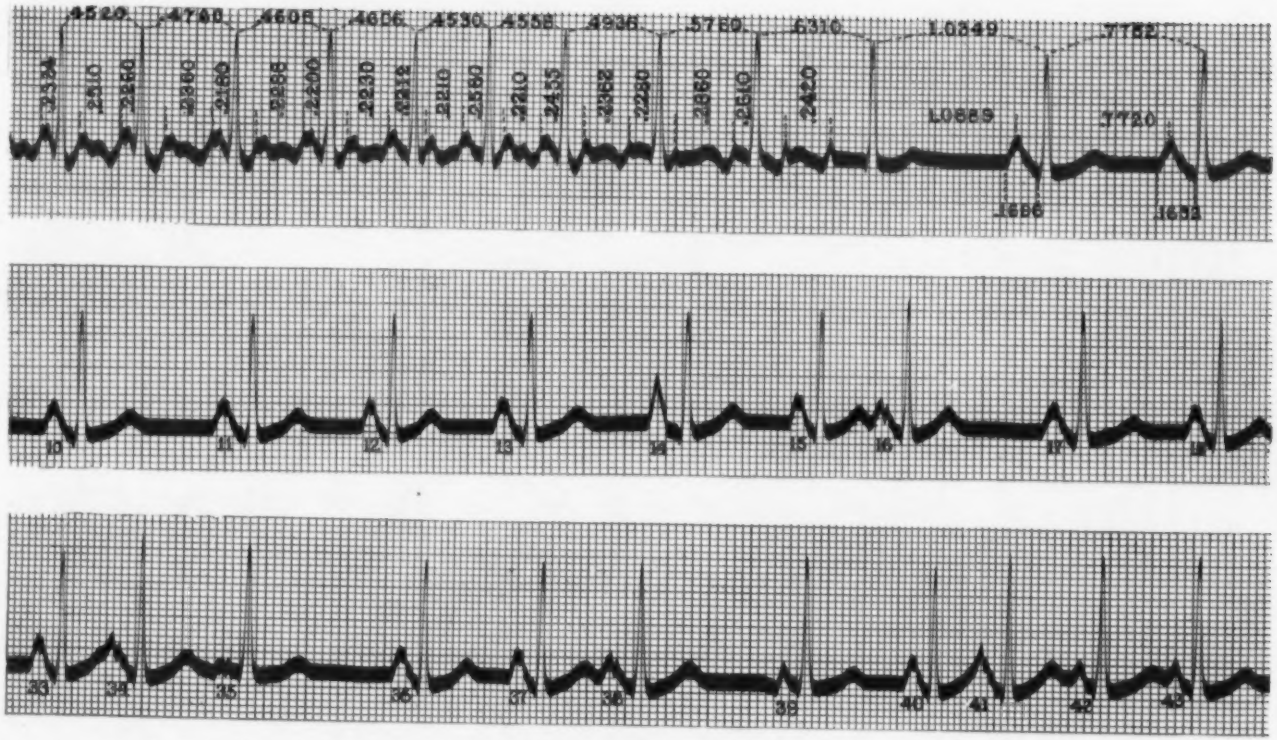

Fig. 5.—Case 2. Hosp. No. 4330. Transition from auricular flutter to normal rhythm (Lead II) with tenth to eighteenth, and thirty-third to forty-third cycles after establishment of sinus rhythm. Occasional auricular premature contractions. (For tabulation of measurements, see Table 2.)

The patient was partly digitalized prior to quinidin therapy, having taken some digitalis, the amount of which was not definitely known, before entering the hospital. He received four courses of quinidin. On two occasions only was the normal rhythm reestablished. The original mechanism was coarse auricular fibrillation, with a ventricular rate of 145.

First Course.—May 13: 1.2 gm. was given in one day. The patient received 0.4 gm. at 10:30 a. m., 12:30 and 2:30 p. m. There was no significant effect.

Second Course.—May 19 to 25: 8.4 gm. were given in seven days. This course was given six days after the first attempt at therapy.

First Day: 0.4 gm. was administered at 10 a. m., 12 noon, 2 and 4 p. m. The ventricular rate before the first dose was 125, somewhat higher than when the first course was given. After 0.8 gm. this had risen to 150. After 1.2 gm. it was again 120 and there were premature beats of right ventricular origin. At 4:35 p. m., i. e., thiry-five minutes after a total of 1.6 gm. had been administered, there was ectopic right ventricular tachycardia with a rate of 120.

Case 3. Hosp. No. 4118

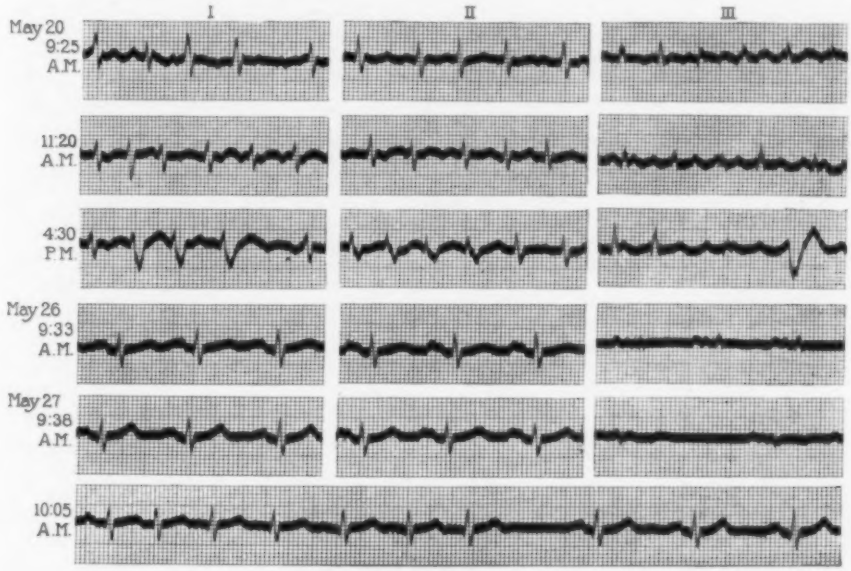

Fig. 6.—Case 3. Hosp. No. 4118. May 20: Quinidin sulphate, 0.4 gm., at 10 a. m., 12 noon, 2 and 4 p. m.

9:25 a. m., control. Auricular fibrillation; ventricular rate 120.

11:20 a. m., after 0.4 gm. Coarser auricular fibrillation; ventricular rate 130.

4:30 p. m., after 1.6 gm. Auricular fibrillation; paroxysms of ventricular tachycardia; isolated left ventricular premature beats.

May 21 and 22: No quinidin given.

May 23 and 24: Quinidin sulphate, 1.6 gm., on each day.

May 25: Quinidin sulphate, 2 gm.

May 26: 9:33 a. m. Normal rhythm; ventricular rate 78; P-R = 0.24 sec.

May 27: 9:38 a. m. Normal rhythm; sino-auricular block; ventricular rate 80; P-R = 0.22 sec.

10:05 a. m. Paroxysm of auricular tachycardia with transition to normal rhythm.

Second Day: The following morning ventricular tachycardia had disappeared and the ventricular rate was 120. Four-tenths gram was again given at 10 a. m., 12 noon, 2 and 4 p. m. At 11:20, one hour and twenty minutes after the first dose, there was impure flutter in addition to the coarse fibrillation. At 1:30, one hour and thirty minutes after the second dose, there was again auricular fibrillation without flutter, but there were right ventricular premature beats. The ventricular rate was 140. At 4:30, thirty minutes after the fourth dose, there were paroxysms of ventricular tachycardia originating first in the right ventricle, then in the left, together with isolated left ventricular premature beats; the rate was 130.

Third Day: There was again auricular fibrillation with a ventricular rate of 126. No drug was given on this day or on the fourth day of treatment.

Fifth Day: 0.4 gm. was given at 11 a. m., 1, 3 and 5 p. m. The ventricular rate at 9:54 a. m., before giving quinidin, was 145; at 4:15 p. m. it was 115. No change in mechanism was noted.

Sixth Day: At 9:27 a. m., there was impure flutter with rate of 130; 0.4 gm. was given at 10 a. m., 12 noon, 2 and 4 p. m. At 1:30 p. m., one hour and thirty minutes after a total of 0.8 gm., had been given, there were right ventricular premature beats. At 3:55 p. m., fifty-five minutes after the third dose, there were paroxysms of left ventricular tachycardia with a rate of 130. At 4:15 p. m. these had disappeared and there were isolated right ventricular premature beats.

Seventh Day: 0.4 gm. given at 9:30 and 11:30 a. m., 1:30, 3:30 and 6 p. m. Electrocardiograms taken on this day showed impure flutter with a ventricular rate ranging from 110 to 130. At about 7 p. m. the normal rhythm was established, the patient being distinctly conscious of the alteration in mechanism. The following morning at 9:33, this was recorded with a rate of 78, the P-R (conduction) time being 0.24 second. The normal rhythm persisted for fourteen days, during which the rate ranged from 75 to 90, and the P-R (conduction) time from 0.21 to 0.24 second. On the second day of normal rhythm an isolated instance of sino-auricular block was photographed, and later on this same day a short paroxysm of auricular tachycardia with the transition to the normal rhythm. On the twelfth and thirteenth days of normal rhythm there were auricular premature beats, and on the fourteenth day auricular fibrillation with rate of 102 was again present. The T wave during the time when normal rhythm was present showed no significant alteration. Fibrillation proceeded for three days, the ventricular rate during most of this period ranging from 150 to 160.

Third Course.—June 16 to 20: First Day: 0.4 gm. given at 10:30 a. m., 12:30 and 2:30 p. m. At 11:30 a. m., one hour after the first dose, there were right ventricular premature beats. At 1:40, one hour and ten minutes after the second dose, there were portions of the curves showing impure flutter in addition to fibrillation, with both right and left premature beats, the ventricular rate being 140. The ventricular premature beats disappeared before the third dose was given but were again present one hour after 1.2 gm. had been administered.

Second Day: Impure flutter with coarse fibrillation still prevailed; 0.4 gm. given at 10 a. m., 12 noon and 2 p. m. At 10:50, fifty minutes after the first dose, the curves showed flutter and impure flutter with a ventricular rate of 160. After the second dose there was again coarse fibrillation with right ventricular premature beats. One hour after the third dose there was again coarse fibrillation with impure flutter and right ventricular premature beats.

Third Day: No quinidin was given. The mechanism was impure flutter with rate of 145.

Fourth Day: No records were made.

Fifth Day: At 9:50 there was coarse fibrillation and impure flutter with a rate of 160; 0.4 gm. given at 11 a. m., 1, 3, 5 and 7 p. m. The rate remained at about this level. At 3:40, forty minutes after the third dose, there were occasional premature beats arising in both right and left ventricles. Fifty minutes later these were more numerous.

Sixth day: A record taken at 9:50 a. m. showed the normal mechanism with a rate of 88, the P-R (conduction) time 0.21 second and an upright T wave in Lead III, it having been previously inverted. At 4 p. m. on this day the rate was 85 and there were occasional auricular premature beats. The duration of normal rhythm was brief, and on the following morning there was again coarse auricular fibrillation with rate of 150 and flattening of the T wave in Lead III.

Fourth Course. June 22: 1.6 gm. were given in one day, 0.4 gm. at 10:30 a. m., 12:30, 2:30 and 4:30 p. m. At 11:30, one hour after administering 0.4 gm., there was, in addition to auricular fibrillation, impure flutter with rate of 180. One hour after the second dose, the rate had fallen to 142, and at 3:36, one hour and six minutes after the third dose, the rate was 125. There were at this time paroxysms of right and left ventricular tachycardia. At 4:25 these paroxysms were no longer noted, nor was impure flutter present. There was coarse auricular fibrillation with isolated right and left premature beats, the ventricular rate being 138.

On the following morning the ventricular rate was 134, and the patient complained of palpitation and dyspnea. He was accordingly given digitalis in the form of digitan, 1 gm. on this day and 0.5 gm. the following morning. No further attempt at quinidin therapy was undertaken.

CASES IN WHICH THE RESTORATION OF THE NORMAL MECHANISM WAS NOT ACCOMPLISHED

CASE 4.—Female, aged 32. Diagnosis: Chronic endocarditis (rheumatic); mitral stenosis and insufficiency; aortic insufficiency. Known duration of fibrillation, five months; duration of cardiac symptoms, two years.

In five days 4.8 gm. was given. The original mechanism was auricular fibrillation, with right ventricular preponderance. The patient was well digitalized before beginning quinidin treatment, the ventricular rate ranging from 70 to 80.

First Day: Feb. 28: 0.2 gm. given at 11:50 a. m. and 5:30 p. m. There was no notable effect.

Second Day: 0.4 gm. given at 12:30 and 6 p. m. There was a sharp rise in heart rate to 142 at 8 p. m. with a gradual return to the former level of 64 the following morning.

Third Day: 0.4 gm. was given at 9:50 a. m., 2 and 6 p. m. Again there was a sharp rise in rate, reaching its maximum of 135 at 8 p. m., with return to 75 by the following morning. There were, in addition, occasional right ventricular premature beats which were first recorded three hours after the first dose on this day, and persisted throughout the night. The following morning the rate was 75.

Fourth Day: 0.4 gm. was given at 7:30 and 11:45 a. m., and 5 p. m. The rate again rose to 127 at 6 p. m. with gradual fall during the night. Right ventricular premature beats persisted.

Fifth Day: The rate in the morning was 82; 0.4 gm. was given at 8 and 11:30 a. m., and 5 p. m. Tachycardia again ensued, with maximum rate of 125 at 8 p. m. Premature beats became more numerous. No more quinidin was administered. The following morning the rate was again 69 to 74.

CASE 5.—Male, aged 19. Diagnosis: Chronic endocarditis (rheumatic): mitral stenosis and insufficiency; aortic insufficiency. Known duration of fibrillation, two months; duration of cardiac symptoms, eight years. The original mechanism was fine auricular fibrillation with right ventricular preponderance, the rate ranging from 63 to 80. During seven days 4.2 gm. was given.

First Day: Feb. 3: 0.1 gm. was given at 12 noon and 5 p. m. No effect was noted.

Second Day: 0.2 gm. given at 11:30 a. m. and 5 p. m. The rate remained 70. There was no significant change.

Third Day: 0.2 gm. at 10 a. m. and 4 p. m. There was a slight increase in heart rate to 104.

Fourth Day: The rate had returned to 60 but there were occasional right ventricular premature beats. No quinidin was given on this day.

Fifth Day: 0.4 gm. was given at 10:30 a. m. and 4 p. m. Three hours after the first dose, the rate was 110, the fibrillatory waves were slightly coarser and there were ectopic beats originating in both left and right ventricles. The T wave was unchanged. At 8 p. m. the ventricular rate was 126 but by the following morning it had fallen to 73.

Sixth Day: The fibrillatory waves were fairly coarse and the premature beats had disappeared; 0.4 gm. was given at 10:15 a. m., 1 and 4:55 p. m. At 11:35, one hour and twenty minutes after the first dose, the rate had risen to 91 and there were occasional right ventricular premature beats. The T wave in Lead III, which was upright, showed a higher voltage than before. At 12:20 the rate was 130, the curve showing auricular fibrillation and impure flutter, and more numerous right and left ventricular premature beats. At 4:25, three hours and twenty-five minutes after the second dose, the rate was 128, the rhythm flutter, and premature beats were present as before. At 4:45 there was again auricular fibrillation and impure flutter with a rate of 122, and at 5:55 reversion to coarse fibrillation with showers of right and left ventricular premature beats.

Case 6. Hosp. No. 4127

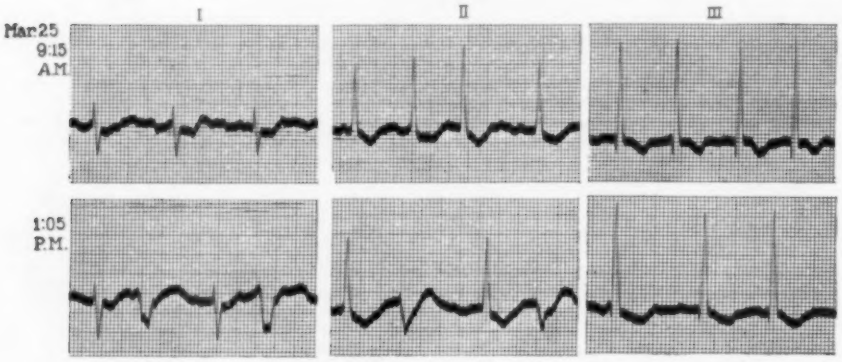

Fig. 7.—Case 6. Hosp. No. 4127. March 25: Quinidin sulphate, 0.4 gm., at 7, 9 and 11 a. m.

9:15 a. m., after 0.8 gm. Auricular fibrillation; ventricular rate 78.

1:05 p. m., after 1.2 gm. Auricular fibrillation; ventricular premature contractions (Leads I and II), coupled with the usual ventricular complexes; ventricular rate 90.

Seventh Day: The ventricular rate at 9:30 a. m. was 70. There was coarse fibrillation with occasional right and left ventricular premature beats; 0.4 gm. was given at 11:30 a. m., 1:30 and 3:30 p. m. There was a gradual increase in rate which at 6 p. m. was 111, but without alteration in mechanism. Coarse fibrillation and right and left ventricular premature beats persisted. On the following day, the tachycardia was still present, the ventricles beating at the rate of 131 at noon. There was also a sharp rise in temperature, which at 4 p. m. was 102 F. Whether or not this febrile reaction bore any relation to quinidin therapy it was not possible to say. At the time at which it occurred the patient complained of severe pain in the precordial region and in the left chest. The following morning the temperature was again normal, the ventricular rate 74. No more quinidin was administered.

Case 6.—Female, aged 23. Diagnosis: Chronic endocarditis (rheumatic); mitral stenosis and insufficiency. Known duration of fibrillation, thirteen months; duration of cardiac symptoms, five years. The patient received two courses of quinidin.

First Course.—Feb. 24 to 28: 3.6 gm. was given in five days. The original mechanism was fine auricular fibrillation with right ventricular preponderance and occasional right ventricular premature beats. The rate ranged from 60 to 80. The patient had been receiving digitalis in the form of digitan for a number of days prior to quinidin therapy.

First Day: 0.2 gm. was given at 12 and 2 p. m. There was no notable effect.

Second Day: 0.4 gm. was given at 7, 9 and 11 a. m., and 1:10 p. m. Two hours and five minutes after the first dose there were numerous right ventricular premature beats which were rhythmically coupled with normal complexes. Fifty minutes after the fourth dose the extrasystoles disappeared and were not again recorded for two days. There was a slight increase in rate, from 78 to 90.

Third Day: The rate was again 74. There were no premature beats. No quinidin was given on this day.

Fourth Day: No quinidin was given.

Fifth Day: The rate at 9 o'clock was 62; 0.4 gm. was administered at 9:20 and 11 a. m., 1 and 3 p. m. At noon, one hour after the second dose, the ventricular rate was 94 and remained at a fairly constant level, between 80 and 90, thirty minutes after the fourth dose. At this time there were paroxysms of ventricular tachycardia with a rate of 115, and right ventricular premature beats of various forms. The paroxysms were still present at 5:45, and at this time left ventricular premature beats as well as others originating in the right ventricle were noted. By the following morning the ventricular rate was again 62 and the original mechanism, namely, fine auricular fibrillation, was present. No quinidin was given for eight days.

Second Course.—April 4 to 6: 3.2 gm. was given in three days.

First Day: 0.4 gm. was given at 11 a. m. and 4 p. m. At 3:15 the rate had risen to 145 and right ventricular premature beats were again present.

Second Day: 0.4 gm. was given at 7:15 and 11:15 a. m. and 4 p. m. The rate remained at a fairly constant level between 80 and 90, but at 4:15 right ventricular premature beats, which earlier in the day had not been present, reappeared.

Third Day: 0.4 gm. was given at 7:15 and 11:20 a. m. and 4 p. m. The rate at 8 a. m. rose to 117, fell gradually to 87 at 6 p. m., but on the following morning was again relatively high, namely from 115 to 125. After a lapse of twenty-four hours, however, the ventricles were beating 73 times per minute. No more quinidin was given.

Case 7.—Male, aged 58. Diagnosis: Chronic myocarditis. Known duration of fibrillation, one month; duration of cardiac symptoms, two years. This patient received 3.2 gm. quinidin in five days. The original mechanism was fine auricular fibrillation with left ventricular preponderance. He had been in the hospital prior to quinidin therapy for one month, during which time he received no medication. The ventricular rate during this time was quite labile, ranging from 90 to 120.

First Day: March 28: The rate at 9:45 a. m. was 120; 0.2 gm. was given at 10 a. m. and 12 noon. At 2:15 p. m. there were right and left ventricular premature beats, which by 4:20 had disappeared.

Second Day: The rate at 9:14 was 112; 0.4 gm. was given at 10 a. m., 12 and 2 p. m. At noon the rate had risen to 140 and there were paroxysms of left ventricular tachycardia with isolated left ventricular premature beats. These paroxysms persisted throughout the day, becoming longer, so that at 5:30 they were almost continuous.

Third Day: No quinidin was given. The record at 9:25 a. m. showed 3:1 auricular flutter. At 10:40 the curve showed both auricular flutter and fibrillation. At 12:10 there was again pure flutter, with an occasional left ventricular premature beat, the ventricular rate ranging from 115 to 120.

Fourth Day: 3:1 flutter, with ventricular rate of 125, was still present at 9:07 a. m.; 0.4 gm. was given at 10:30 a. m. and 2 p. m. At 11:38 there was once again auricular fibrillation and flutter, and at 1:15, 2:1 flutter with ventricular rate of 145. This mechanism persisted throughout the day until

4 o'clock, at which time there was 2:1 flutter, with paroxysms of left ventricular tachycardia.

Fifth Day: At 9:05 a. m. the curve showed both impure flutter and fibrillation; 0.4 gm. was given at 10:10 a. m. and 2 p. m. At 11:30, one hour and twenty minutes after the first dose, there was 3:1 flutter with ventricular rate of 112. At 4:10, two hours and ten minutes after the second dose, there was 2:1 flutter with paroxysms of left ventricular tachycardia, ventricular rate being 132. A record made at 5:05 showed the persistence of this mechanism. On the following morning the flutter was still present, the ventricular rate being 120. Digitalis, in the form of digitan, 0.5 gm., was given at 10 a. m. and again at 11 a. m. At 11 o'clock there was auricular flutter and fibrillation, with a ventricular rate of 122. On the day following the administration of digitan, the ventricular rate was 80, and fine fibrillation, as it had appeared before beginning quinidin treatment, was again the prevailing mechanism.

Case 8.—Male, aged 34. Diagnosis: Chronic endocarditis (rheumatic); mitral stenosis and insufficiency. Known duration of fibrillation, three weeks; duration of cardiac symptoms, one and one-half years. The original mechanism

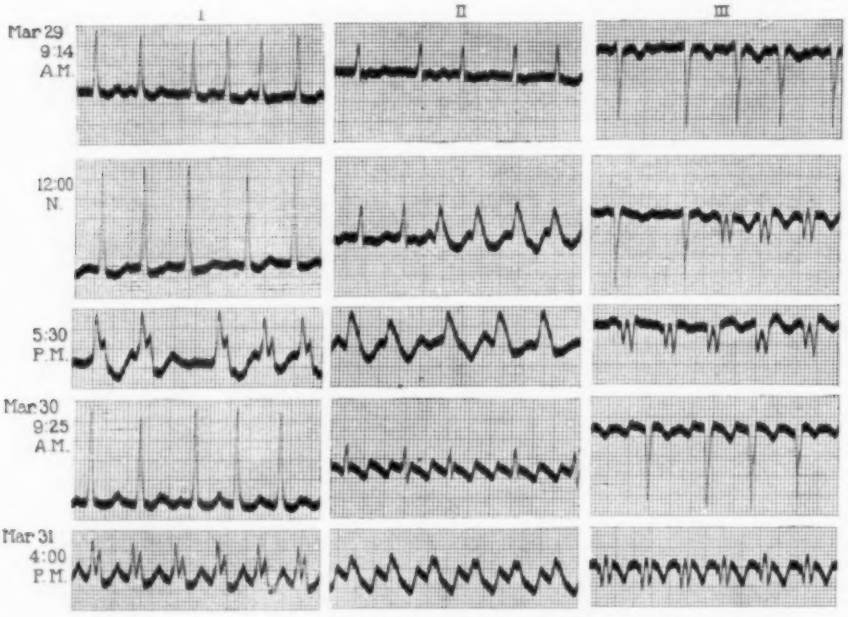

Fig. 8. Case 7. Hosp. No. 4327. March 29: Quinidin sulphate, 0.4 gm., at 10 a. m., 12 noon and 2 p. m.

9:14 a. m., control. Auricular fibrillation; ventricular rate 112.

12:15 p. m., after 0.8 gm. Auricular fibrillation; paroxysms of left ventricular tachycardia.

5:30 p. m., after 1.2 gm. Same as 12 noon. Longer paroxysms of tachycardia.

March 30: No quinidin given.

9:25 a. m. Auricular flutter; ventricular rate 115; auricular rate 345.

March 31: Quinidin sulphate, 0.4 gm., at 10:30 a. m. and 2 p. m.

4:00 p. m., after 1.2 gm. Auricular flutter; paroxysms of left ventricular tachycardia; ventricular rate 135; auricular rate 270.

was fine auricular fibrillation. The patient had been in the hospital two weeks prior to quinidin therapy without medication, during which time the ventricular rate ranged from 90 to 110; 6.2 gm. quinidin was administered during an eight day period.

First Day: March 30: 0.2 gm. given at 2 and 4 p. m., with rise of ventricular rate from 94 to 105.

Second Day: At 9:26 a. m. the rate was 104 and there were occasional left ventricular premature beats; 0.4 gm. was given at 10:15 a. m., 12 noon and 2 p. m. At 11:30 the fibrillatory waves had become somewhat coarser and the rate was 110; at 2:05 the rate was 135. At 4:15 p. m. there was impure flutter with a ventricular rate of 120.

Third Day: At 9:16 a. m. the record showed coarse fibrillation and impure flutter with a ventricular rate of 112. The T wave in Lead II, which had previously been upright or diphasic, was now iso-electric; 0.4 gm. was given at 10:25 a. m., 12 noon and 2 p. m. At 11:52 there was impure flutter with right ventricular premature beats, and this persisted throughout the day, the ventricular rate ranging from 90 to 120. The T waves in Leads II and III were variable.

Fourth Day: At 9:42 the ventricular rate was 90 and there was coarse auricular fibrillation. The T wave in Lead III, which had before been inverted, was now upright. Only one dose of quinidin, 0.4 gm., was given at 10 a. m. because of complaint by the patient of epigastric discomfort.

Fifth Day: No quinidin was given.

Sixth Day: The ventricular rate was 120; 0.4 gm. was given at 7:30 and 11:45 a. m., and 5 p. m. There was no significant change in mechanism but the rate fell gradually to 90 at 3:35 p. m. The T wave in Lead III again was variable in its direction.

Seventh Day: The ventricular rate was 115, the records showing coarse fibrillation; 0.2 gm. was given at 10:10 a. m., 2, 4, 6 and 8 p. m. This smaller and more fractionated dosage produced no notable effects.

Eighth Day: The ventricular rate was 120. There was coarse fibrillation; 0.4 gm. was given at 10:15 a. m. and 12 noon. There was no alteration in mechanism. Headache, slight nausea, sweating and palpitation induced discontinuation of therapy.

Case 9.—Female, aged 33. Diagnosis: Chronic endocarditis (rheumatic); mitral stenosis and insufficiency. Known duration of fibrillation, two months; duration of cardiac symptoms, seven years.

This patient received 2.4 gm. quinidin in three days. The original mechanism was moderately coarse auricular fibrillation with occasional left ventricular premature beats. The ventricular rate prior to therapy ranged from 95 to 140.

First Day: March 31: 0.2 gm. was given at 11:30 a. m. and 12:30 p. m. There was no noteworthy effect.

Second Day: The rate at 9 a. m. was 112. No ventricular premature beats were recorded; 0.4 gm. was given at 10:20 a. m., 12 noon and 2 p. m. At 12 o'clock the rate had risen to 130 and there were numerous left ventricular premature beats. At 2:45 impure flutter was present, with a ventricular rate of 170. At 4:45 there was impure flutter and coarse fibrillation, with a ventricular rate of 110.

Third Day: The ventricular rate at 9:12 a. m. was 155, with occasional left ventricular premature beats; 0.4 gm. was given at 10 a. m. and 12 noon. There was no alteration in mechanism. The patient complained of severe headache and of precordial pain. On the following day digitan, 0.5 gm., was given at 11:30 a. m. and again at 12:30 p. m. Twenty-four hours later the ventricular rate was 62. Electrocardiograms showed a finer fibrillation than had previously been noted at any time.

Case 10.—Female, aged 46. Diagnosis: Chronic endocarditis (rheumatic); mitral stenosis and insufficiency; aortic insufficiency. Known duration of fibrillation, three weeks; duration of cardiac symptoms, four months. The original mechanism was fine auricular fibrillation. This patient received three courses of quinidin. Prior to the first course her heart had been brought fairly well under the influence of digitalis, the ventricular rate ranging from 78 to 100.

First Course.—April 5 to 8: Three gm. was given in four days.

First Day: The ventricular rate at 9:45 was 90; 0.2 gm. was given at 12 and 3 p. m. At 4:55 the ventricular rate was 110 and there were right ventricular premature beats.

Second Day: 0.2 gm. was given at 7:30 a. m., 12 noon and 4:30 p. m. There was no noteworthy change in rate or mechanism.

Third Day: 0.4 gm. was given at 7:30 and 11:30 a. m. At 9:19 ventricular rate was 110 and the T wave in Lead I, which had previously been upright, was inverted; at 4:25, the rate was 120.

Fourth Day: The ventricular rate at 9:08 a. m. was 100; 0.4 gm. was given at 10:35 a. m., 12:30 and 2:45 p. m. There was a sharp rise in heart rate to 140 at 2:10 p. m., with gradual fall after 4 p. m. to 84 the following morning. The patient at this time was distinctly uncomfortable. She was dyspneic, the liver was large and tender, there was epigastric discomfort, and there had been,

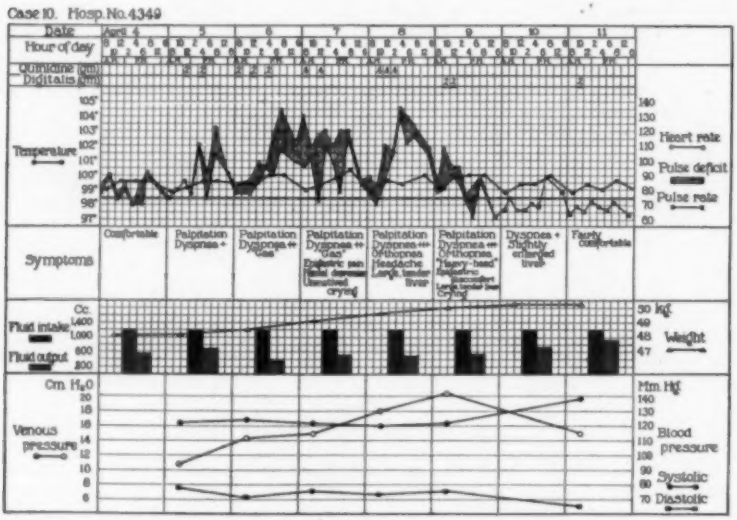

Fig. 9.—Case 10. Simple tachycardia induced by quinidin was followed by signs and symptoms of heart failure. Digitalis afforded prompt relief.

during the ten days preceding, a gradual gain in weight. Therefore during the next two days she was given a course of digitalis therapy with prompt disappearance of symptoms and improvement in signs. The heart rate fell to about 70 and there was no pulse deficit. Small doses of digitalis were continued thereafter for sixteen days.

Second Course.—April 27 to 29: On the seventeenth day after the first course was completed, the second course began; 1.6 gm. was given during a three day period.

First Day: The ventricular rate ranged from 60 to 70; 0.2 gm. was given at 12:25 and 2 p. m. There was no noteworthy effect.

Second Day: No quinidin was given.

Third Day: The ventricular rate was 55; 0.4 gm. was given at 10:30 a. m., 2:30 and 4:30 p. m. At 4 p. m. there were occasional right ventricular premature beats. At 6 p. m. the rate had risen to 132, but fell gradually during the night to its former level of 60 to 70. For three days no more quinidin was administered.

Third Course.—May 2 to 6: Four grams was given during a five day period, and at the same time the patient received 0.1 gm. digitan each day.

First Day: The ventricular rate was 54. The mechanism was fine fibrillation as before; 0.4 gm. was given at 10 a. m., 12 noon and 2 p. m. Once again there was a sharp rise in the ventricular rate to 132 at 4 p. m., with gradual subsidence of the tachycardia and resumption of a rate of 50 the following morning.

Second Day: No quinidin was given.

Third Day: 0.2 gm. was given at 10 a. m., 12 noon and 2 and 4 p. m. No significant effect in mechanism or rate ensued.

Fourth Day: The ventricular rate was 62; 0.2 gm. was given at 10:30 a. m., 12:30, 2:30, 4:30 and 6:30 p. m. Again, there was no change in rate or mechanism. The T wave in Lead I, which previously had been upright, was now iso-electric.

Fifth Day: The ventricular rate was 62; 0.2 gm. was given at 10:30 a. m., 12:30, 2:30, 4:30 and 6:30 p. m. As before this greater fractionation of dosage caused no effect on rate or mechanism.

CASE 11.—Male, aged 55. Diagnosis: Chronic myocarditis. Known duration of fibrillation, seven months; duration of cardiac symptoms, one and one-half years. The patient was well digitalized before beginning therapy. He received two courses of quinidin. His ventricular rate prior to quinidin administration ranged from 66 to 75. The original mechanism was fine auricular fibrillation with left ventricular preponderance.

First Course.—June 1 to 3: 3.2 gm. was given in three days.

First Day: 0.2 gm. was given at 1:40 and 3:40 p. m. There was no demonstrable effect.

Second Day: 0.4 gm. was given at 11 a. m., 1 and 3 p. m. There was no significant effect.

Third Day: 0.4 gm. was given at 10 a. m., 12 noon, 2 and 4 p. m. There was a slight rise in the ventricular rate, from 80 to 108 at 6 p. m. No drug was given during the next two days.

Second Course.—June 6 to 10: 6.8 gm. was given in five days.

First Day: 0.4 gm. was given at 10 a. m., 12 noon, 2 and 4 p. m. There was a slight rise in ventricular rate, from 74 to 94.

Second Day: 0.4 gm. was given at 10 a. m., 12 noon, 2 and 4 p. m. The ventricular rate rose from 82 at 9:50 a. m. to 105 at 3 p. m., and there were a number of left ventricular premature beats. At 4:30 p. m., thirty minutes after the fourth dose, there were paroxysms of left ventricular tachycardia in addition to coarser fibrillatory waves in the remainder of the electrocardiograms and a number of isolated left ventricular premature beats.

Third Day: Paroxysms of ventricular tachycardia were not present in the morning. The ventricular rate was 88; 0.4 gm. was given at 9:30 and 11:30 a. m., 1:30 and 3:30 p. m. At 12:33, one hour and three minutes after the second dose, there were again paroxysms of left ventricular tachycardia with a rate of 100, and isolated left ventricular premature beats. The same mechanism was again present at 4:30 p. m. with a rate of 92.

Fourth Day: Paroxysms of tachycardia no longer were present. There were occasional left ventricular premature beats. The ventricular rate was 82; 0.4 gm. was given at 11 a. m., 1, 3 and 5 p. m. There was a distinct rise in the ventricular rate, which at 8 p. m. was 128. Left ventricular premature beats persisted.

Fifth Day: The ventricular rate was 104; 0.4 gm. was given at 11:20 a. m. At 2 p. m. the ventricular rate was 118 and the patient was decidedly uncomfortable. He complained of palpitation, some precordial pain, heaviness of his head and of vague epigastric discomfort. His temperature at this time rose to 101 F. At 2:15, therefore, digitalis therapy was begun, with prompt reduction in rate to 69 the following day, with subsidence of fever and relief of symptoms.

A STUDY OF THE ERYTHROCYTE CURVE AT VARIOUS AGES AND ITS RELATIONSHIP TO HEMOGLOBIN CURVE

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Numerous studies made on the blood of new-born infants have fairly well established the fact that the number of their erythrocytes per cubic millimeter is much higher than it is in the adult. Furthermore, a review of the results of hemoglobin determinations in new-born infants shows a much higher hemoglobin content than is found in adult life. The high hemoglobin content rapidly falls.

Williamson, in a spectrophotometric analysis of 919 cases, shows in his tables that the hemoglobin of the new-born infant averages 23.2 gm. hemoglobin per hundred c.c. of blood. The hemoglobin falls rapidly and by the end of the second month the reading is 18.3 gm. At the end of the fifth month it is 13.7 gm., and then remains practically constant during the next few months, falling to 12.5 gm. at the end of the first year. From this point up to the sixth year there is a steady ascent, when it approximates the height of adult life.

Several factors, singly or in combination, may be the cause of this fall, i. e., a sufficient decrease in the number of corpuscles or a decrease in the hemoglobin or a combination of both phenomena. For a study of the problem it was necessary to establish this variation in relation to color index of new-born infants and for the early days and months of their lives. Periods conforming to the age periods of the hemoglobin curve were selected for comparison.

Burker's Zeiss hemocytometer,[1] an approved apparatus for the more accurate counting of erythrocytes than is possible by the Thoma-Zeiss apparatus, was used in all the counts. The principles involved are somewhat different from those in force with the latter apparatus. Hayem's solution is used as the diluting fluid. Toison's solution is not satisfactory for use with the Burker counting chamber as its viscosity is too great. The corpuscles settle rapidly in Hayem's fluid as the specific gravity of the fluid is 1.015, whereas that of the erythrocytes is 1.090. The Thoma-Zeiss capillary pipets were used. The blood was thoroughly mixed with the diluting fluid within the mixing chamber by tapping the pipet against the finger for five minutes.

In the older counting chamber the floor of the chamber is circular and the counting is done in the center of this space. The corpuscles are, therefore, counted in the center of a capillary circular film, where, on account of surface tension, their number is slightly greater than elsewhere. This source of error is avoided in the new counting cham-

1. Burker: Pflüger's Arch. f. d. ges. Physiol. **107**:426, 1905.

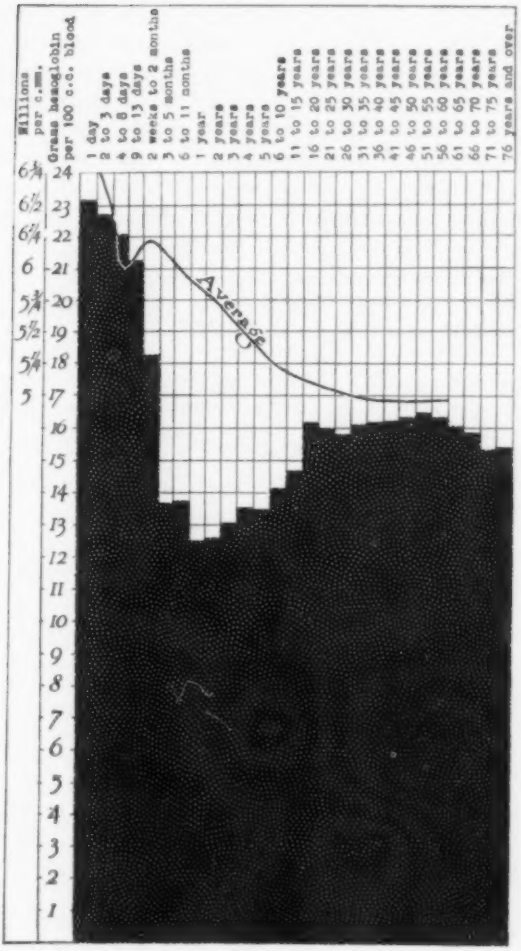

Fig. 1.—The solid black line indicates grams of hemoglobin per 100 c.c. of blood in persons ranging in age from one day to over 76 years. The curved line shows the average erythrocyte count at different ages to show the relationship between the number of erythrocytes and their hemoglobin content.

ber, in which the floor is represented by the upper surface of a glass 25 mm. long and 5 mm. wide, which is rounded off at both ends and divided into two portions by a groove 1.5 mm. wide through the center. At each side of the floor piece, separated from it by a groove, is a glass plate 7.5 mm. x 21 mm., of such height that the space between the floor of the cell and the cover glass placed across the plates is 0.100 mm. A cover glass 23 mm. long and 21 mm. wide, with rounded, polished edges, is used, so that the rounded edges of the floor project beyond it. The chamber is provided with clamps to press the cover glass firmly on both plates. The same pipets, counting chamber and cover glass were used in all this series of counts.

To determine the accuracy of my blood enumeration, I counted my own blood for five counts over a period of seven hours. Eighty squares were counted. The result of the counts and a computation of the average error by method of Gauss was as follows:

Let d equal the variation from the average.
Let Sd^2 equal the sum of the squares of the individual variations.
Let Fm equal the average error of the average value.
Let N equal the number of observations.

No. of Count		d a	d^2
1	530	+1	1
2	528	−1	1
3	531	+2	4
4	529	0	0
5	530	+1	1
529	Average		7 Sd^2

$$F\,M = \pm \frac{Sd^2}{n-1} \pm \frac{7}{4} = 1225 = \pm 1.1$$

As a further check to determine the variation of the blood from day to day, my blood was counted for seven consecutive mornings.

No. of Count			Sq. of Difference from Average
1	504	+ 7	49
2	471	−26	676
3	510	+13	169
4	503	+ 6	36
5	529	+32	1024
6	460	−37	1369
7	501	+ 4	16
Av.	497		6 | 3339
			556

$$\sqrt{556} = \pm 23.6$$

The average error $= \pm$ the $\sqrt{\frac{S\,D^2}{N-1}}$ in which $S\,D^2$ is the sum of the square of the differences of the individual counts from the average count and N = the number of counts. Number of counts is seven.

$$\text{Average error} = \pm \sqrt{\frac{S\,D^2}{N-1}} = \frac{3339}{6} = \pm 23.6$$

Blood was obtained from the right great toe in each instance. The toe was washed with alcohol and thoroughly dried. A sharp cataract knife was used to get a free flowing drop, without pressure. The first drop was wiped away and blood for the counting secured from the second drop. The children chosen were all apparently well nourished and healthy. The cases were taken from the maternity wards of Cook County and St. Luke's Hospitals and from private cases.

It is generally conceded that there is a polycythemia at birth and that there is an increase in the first twenty-four hours. There is much diversity of opinion as to the actual number found in a cubic millimeter of blood. The average number of red blood corpuscles per cubic millimeter based on the investigations of physiologists and pathologists, is 5,742,000 red blood corpuscles per cubic millimeter of blood. The majority of the workers' conclusions for infants were based on comparatively few cases. Hayem [2] and Sorensen cite one case each. Buchot and Dubrisay [3] show 4,300,000 as an average in six cases; Otto,[4] four cases averaging 6,165,000; Schwinger,[5] 5,080,765 and Schiff,[6] 5,825,000 in single counts. Fehrsen [7] observed forty cases—minimum 6,047,000, maximum 7,250,000. The majority of these observers used the dilution method and counted with a Thoma-Zeiss apparatus. Fehrsen's forty subjects were examined on the first and tenth days of life. Only four subjects were examined within the first two hours and nineteen were examined between the tenth and twentieth hours, with an average of 5,898,000. Woino and Dransky [8] observed twenty-nine cases. Seven of these were not at full term and five were pathological. Six counts were made on babies before they began to breathe. His conclusions are in general similar to those of Hayem, Lepin and Schiff, namely, the number of red cells per cm. in the newborn is considerably higher than in adults and figures exceeding 7,000,000 were often obtained. He was unable to confirm the statement of Hayem and Lepin about the strict dependence between the changes in the number of red cells and the weight of the infant. This bears out my own conclusions, as I observed no relation between the number of red cells and the weight of the infant.

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2. Hayem, Georges: Du Sang et de ses alterations anatomiques, Paris, 1889, pp. 30 et seq.; 189.
3. Buchot and Dubrisay: Gaz. méd. de Par. 168, 1878.
4. Otto, R.: Pflüger's Arch. f. d. ges. Physiol. **36**:12, 27, 1885.
5. Schwinger, W.: Untersuchungen über den Hämoglobin Gehalt u. d. Zahl der rothen und weissen Blutkörperchen, Pflüger's Arch. f. d. ges. Physiol. **72**: 299, 338, 1898.
6. Schiff, E.: Ztschr. f. Heilk. **11**:17, 1890; ibid. **10**:, 1890.
7. Fehrsen, O. M.: Hemoglobin and Corpuscular Content of the Blood of the Newborn, J. Physiol. **30**:322, 1903.
8. Woino and Dransky: Beiträge zur Morphologie des Blutes der Neugeborenen. Dissertation, St. Petersburg, 1891.

In my own series of forty-one cases, I found an average of 7,630,000. Thirty-seven were taken at the time of delivery and four within two hours of delivery. Ten cases were counted on the second, eighth and fourteenth days, with an average of 6,260,000.

10 cases	14th day.....	Averaged	5.790		
10 "	One year	"	5.850	(Boys and Girls)	
10 "	Two years	"	5.750	" "	"
10 "	Five to ten years.....	"	5.210	" "	"

The highest count was 9,610,000 and the lowest was 5,060,000. The findings are expressed graphically in Figure 1, which shows, in solid black, the number of grams of hemoglobin per hundred c.c. in persons ranging in age from 1 to 76 years; and in the curved line, the average erythrocyte count at the same ages. In Figure 2, lines 1, 2 and 3 represent the average, maximum and minimum red blood corpuscle count in a series of forty-one cases. Lines A, B and C show the average, maximum and minimum of hemoglobin, represented by the number of grams of hemoglobin per hundred c.c. of blood.

The hemoglobin richness of the individual red corpuscles is known as its color index. The amount of coloring matter, i.e., hemoglobin, expressed in grams per hundred cubic centimeters, in normal blood, is considered to represent 100 per cent. The average normal red cell count, i. e., 5,000,000 for males and 4,500,000 for females, is considered 100 per cent. The color index is determined by dividing the percentage of hemoglobin by the percentage of red cells. In normal blood the color index is 1.

It is at once evident that four factors enter into each estimation of color index. Two of them are constants and two of them are variables, which must be accurately determined in each case. The constants are: (a) The normal average number of red cells per cubic millimeter of blood; (b) the normal average number of grams of hemoglobin per hundred cubic centimeters of blood. The variables are: (c) The actual number of red blood corpuscles per cubic millimeter of blood; (d) the actual number of grams of hemoglobin per hundred cubic centimeters of blood in any case under consideration.

If the results of different observers are to be compared, the same standards for constants must be employed. The averages that are recognized in the computation of color index in adults cannot be employed in determining the color index of children. It is immediately manifest, when one consults the hemoglobin values as established by Williamson's table,[9] that the determination of color index in children is only possible when the proper number of grams of hemoglobin for the age of the child is employed as 100 per cent. Similarly, the average

9. Williamson: Arch. Int. Med. **18**:505 (Oct.) 1916.

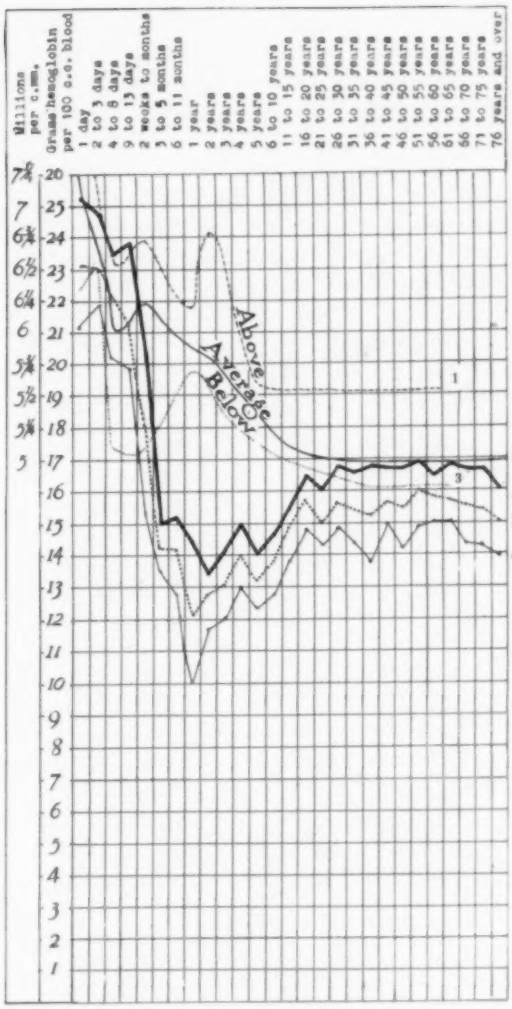

Fig. 2.—Lines A, B and C indicate the average amount of hemoglobin, and the average amount for those having more than the average and also for those having less than the average, for males ranging in age from 1 day to over 76 years. Lines 1, 2 and 3 show the average number of erthyrocytes and the average number for those having more than the average and for those having less than the average.

number of red cells obtaining for that age must likewise be employed as representing 100 per cent. In adult males the ordinary procedure of using 5,000,000 reds and 16 gm. hemoglobin is so nearly constant that these figures may be considered normal and will not give appreciable variations. The actual normal fluctuations in early life make the use of any average impossible.

CONCLUSIONS

1. The red blood count in a series of forty-one infants, in thirty-seven of whom it was taken at time of delivery, averaged 7,630,000.

2. The blood count in children 1 and 2 years of age is somewhat higher than in the adult, this being in marked contrast to the great drop in hemoglobin which is shown in Williamson's table.

3. Inasmuch as the curves of corpuscles and the hemoglobin do not run parallel to each other, the question is raised as to whether the low hemoglobin values are to be regarded as strictly normal or whether it might be altered by a different plan of infant feeding.

4. The norm employed in determining the color index of adults does not apply in determining the color index of children under 10 years of age.

INTRAVITAM BONE MARROW STUDIES
PRELIMINARY REPORT

PART I

DESCRIPTION OF A MARROW TREPHINE AND EXPERIMENTAL STUDIES *

LAIRD M. MORRIS, M.D., AND ERNEST H. FALCONER, M.D.
SAN FRANCISCO

During the latter part of 1920 one of us (L.M.M.) devised a small drill carrying an outer detachable casing, the purpose of which was to trephine long bones in order to secure specimens of living bone marrow for histologic study. The problems which were opened to approach by this new method of study were undertaken jointly in 1921.

To G. Ghedini [1] is conceded the credit of marrow puncture for diagnosis and prognosis. In 1910 he elaborated on this method of diagnosis in certain diseases of the blood and presented to the profession a most comprehensive article based on his experience and that of others regarding the importance of his procedure. He concludes some facts of primary importance; namely, that disease of the hematopoietic system can occur without changes in the blood and that there are many variations between bone marrow findings and those of the blood. That furthermore, severe pathology could be present for some time in the hematopoietic system without changes in the blood picture, either pre-existing, accompanying, or following; and that the frequency of such an occurrence makes old statistics unreliable because of missed cases. He advocates marrow puncture as a useful procedure.

Since this method was advocated, we have found references in some of the continental publications to bone marrow trephine as a method of diagnosis in certain atypical blood diseases, but the English and American literature is decidedly lacking in the realization of the importance of this procedure. We feel that our experience with marrow puncture, although small, might aid in placing this method before the profession.

The pathologic conditions involving bone marrow and the diseases in which bone marrow punctures might supply information of value were considered carefully. Should the method prove practical, it might be used in (1) the various types of acute and chronic leukemias; (2) atypical leukemias, chloroma and pseudoleukemia; (3) pernicious

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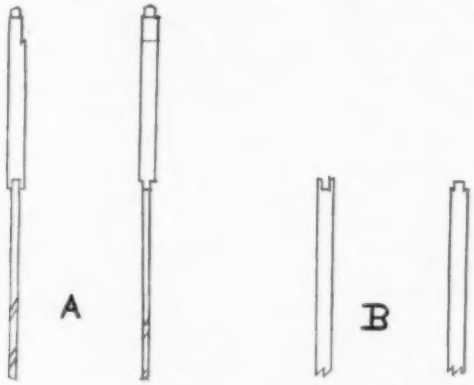
1. Ghedini: Wien. klin. Wchnsch. **23**:1840, 1910.

anemia; (4) aplastic anemia, unclassified anemias, anemias due to sepsis, toxic agents, and invasion of marrow by tumor formation; chronic hemolytic jaundice and osteosclerotic anemia; (5) polycythemia and (6) purpura and allied conditions.

With this field in mind, obviously the first step was to try out the feasibility of this procedure by animal experimentation. For this, an instrument smaller but identical to the one described herein and driven by a reciprocating hand drill was used.

DESCRIPTION OF MARROW TREPHINE

The small trephine instrument as reproduced in the accompanying illustration is drawn to scale and represents the type used on human beings for tibia puncture. The drill proper, an ordinary steel drill (detempered), is embedded in a solid steel base, the diameter of which is identical with the standard base of an ordinary dental drill. The casing B bored from a solid steel tube of the same



Bone marrow trephine. A—Drill. B—Casing.

diameter is of slightly shorter length than the naked drill proper and fits it snugly. The proximal circumference is longitudinally cut and fits identically into opposite grooves cut in the distal circumference of the base, into which the drill proper is set. The distal circumference of the casing is toothed and sharpened and cuts simultaneously, the drill proper preceding the casing about one-eighth of an inch. The bone dust is forced up the grooved drill inside the casing.

Technic.—Both the drill proper and the casing pierce the cortex of the bone and enter the marrow cavity. The drill is then removed, leaving the casing in the marrow cavity and protecting the same from blood or other cellular tissue. In this way it is possible to obtain an uncontaminated marrow specimen. A lumbar puncture needle with approximately a third of the diameter longitudinally grooved has been used to ream the marrow confined within the lower portion of the casing as it rests in the marrow cavity. The drill is driven by a dental engine, the puncture being readily accomplished by high speed and slight pressure. A skin incision about 1 cm. in length precedes the application of the drill to the bone (tibia). The entire operation is performed under local anesthesia. Silk is used to close the skin wound.

We endeavored to prove two points. First, that living rabbits subjected to bone marrow puncture will show no untoward effects from such an operation. Second, that marrow specimens scooped through the casing limiting the trephine opening will by histologic study reveal the true physiologic or pathologic condition of the marrow. (This attempt is obviously limited to the cytology only.)

From a series of six healthy rabbits, the blood pictures of which totaled within normal limits for red and white blood cells and differential counts,[2] femur punctures were made under aseptic conditions and the marrow smears studied histologically.

Technic for Marrow Smears and Cultures.—The marrow specimen removed from the casing is small in amount and dries quickly when exposed to the air. To insure against cellular distortion we smear the marrow specimen immediately after its withdrawal upon sterile cover slips; float face downward in methyl alcohol for fixation and stain by May-Grünwald-Giemsa and Wright's methods. For section comparison, Wolbach's modification of the Giemsa method or a combination of May-Grünwald and Giesma stains was used after the fixed marrow (two parts saturated mercuric chlorid solution and one part absolute alcohol) had been run down to water and immersed in methyl alcohol.

For cultural work we attempted aspiration of the marrow by a Luer syringe with a nonbeveled needle. Difficulty was always encountered in aspiration; usually the specimen contained much blood and little marrow. Such specimens may be used for marrow cultures in bacteriologic work but are decidedly unfit for histologic study. Thus far we have used the more common culture mediums in our attempts to grow organisms from such preparations.

The puncture wounds healed without infection in about two weeks. The animals were then killed by ether inhalation. Superficial examination at the site of the small trephine opening showed healing of advancing degrees. In no case was the pathologic picture at the trephine site of any marked importance as noted by the unaided eye. In a single case the wound (superficial) was infected, but the bone and marrow cavity was uninvolved.

In all cases the marrow was fixed and studied in section and compared with the smears obtained during life. The smears resembled the marrow sections as to cell type and content. Allowance, however, was made in smear preparations for mature red blood cells present, which are constant and vary according to the number of ruptured sinuses produced by trauma in obtaining the marrow.

2. There is much normal variation in rabbit's blood.

Bunting's [3] experiments on rabbits poisoned with saponin were repeated, in part, with successful blood pictures of blastic crises. Such a series of experiments gave opportunity to study erythrogenic activity in both megaloblastic and normoblastic phases. Both marrow smears and subsequent sections showed a profound action of the poison on the erythroblastic tissues. The activity of the red cell elements was more marked the longer the animal was kept under the influence of nonlethal doses of the marrow toxin. In all cases an experimental anemia was produced, giving pictures of blastic crises whenever saponin was injected intravenously.

Following these experiments, we undertook others designed for more careful study of red blood cell activity. Selling's [4] work on rabbits with benzol was reproduced, in part. When a leukopenia of from two to three thousand per c.mm. is produced, then injections of saponin bring forth blastic activity in the blood interpreted as a profound toxic action on the marrow. The regenerative activity approaches a purer type of small and large premature red blood cell elements, the leukoblastic cells being held largely in abeyance by the toxic action of benzol. It was felt that by so doing a histopathologic marrow picture simulating primary anemia might be approached more closely.

In our study of the white blood cell elements we produced continued leukocytosis over varying periods of time by making subcutaneous abscesses (turpentine) or infection of the peritoneum. In one rabbit small injections of staphylococcus were given intravenously daily. In some animals we were successful in producing a fairly marked (from 14,000 to 15,000) leukcocytosis for a week or more.

Our interpretation of the marrow smears and sections led us to believe that the leukopoietic elements were in predominance, certainly in marked contrast to the experiments with saponin. The marrow smears and sections checked well. None of the animals showed untoward results, although one rabbit was subjected to puncture four times at two-day intervals for study of the developmental myelocytoses. One animal sustained a spontaneous fracture of the femur in this series.[5]

Such preliminary work gave opportunity to study both white and red blood cell activity in the bone marrow by study of smears obtained

3. Bunting: J. Exper. M. **6**:624, 1906.
4. Selling: Beitr. z. path. Anat. u. z. allg. Path. **51**:576, 1911.
5. We attempted no work on fowl leukemia. It was felt that such a condition might well be diagnosed from a marrow puncture, realizing in the pathology of the disease a marked myeloid hyperplasia in the bone marrow.[6]
6. Ellermann: Verhandl. d. Deutsch. Path. Gesellsch. **12**:224, 1908. Ellermann & Bang: Ztschr. f. Hyg. u. Infectionskr. **63**:231, 1909. Schmeisser: J. Exper. M. **22**:820, 1915.

from the same and to check such preparations against microtome sections of the same marrow in the same phase of white or red celled hyperplasia.

These preliminary experimental studies lead directly to the field of marrow pathology in the human, more particularly cellular activity in the long bones.

CONCLUSIONS

1. An instrument has been devised for perforating the cortex of the long bones in animals and human beings to obtain specimens of living marrow for histological study.

2. We have demonstrated on animals that the method is feasible and safe.

3. We feel that the specimens of marrow obtained by this method are satisfactory for microscopic study, but occasional dilution with blood makes the specimen difficult to interpret. The smears from the marrow checked up with postmortem preparations fixed and sectioned.

INTRAVITAM BONE MARROW STUDIES

PART II

SURVEY OF THE CLINICAL FIELD*

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SAN FRANCISCO

In Part I we demonstrated that bone marrow puncture in animals is a comparatively simple and harmless procedure and that it is a feasible and practical method of studying (in rabbits) both normal and pathologic bone marrows, yielding nearly as much information as fixation and sectioning of marrow obtained postmortem. Before proceeding to the clinical application of this method, on the patient, it became necessary to satisfy ourselves regarding certain questions that were uppermost in our minds during the experimental work.

1. *Can the puncture be accomplished without pain and discomfort to the patient and is it safe?*—After trying it out several times on cadavers, we became convinced that the cortex of the tibia could be pierced easily and quickly. We felt that it would be a simple matter to anesthetize the skin and periosteum so that the procedure would be practically painless. The question of safety will be dealt with later but, of course, the final answer can only be given after the method has been tried in a large series of cases.

2. *Can enough accurate data be obtained by this method to offset a certain amount of unavoidable discomfort to the patient and what will the patient benefit by this method of study?*—In order to answer the first part of this question, it was necessary to peruse the literature on the anemias and the leukemias to ascertain whether previous investigators had felt a need for this procedure in the course of their studies and, above all, to find reported cases in which we felt that this method would have supplied the data necessary to make a diagnosis during life. Several of these reported cases are included in this communication. We believe that in certain types of cases it is necessary to know what is taking place in the marrow in order to arrive at a correct diagnosis. Regarding the possible benefit to the patient, it must be acknowledged that in the majority of cases it will not affect the final issue. Yet it must be conceded that it is only by accurate study and recognition of bone marrow pathology during life that we can hope to arrive at means for influencing such pathology.

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3. *Will this method be of distinct advantage over present methods of study and research in investigation of diseases of the hematopoeitic system?*—The question is largely theoretical but we wish to point out what seems to be a distinct advantage over past methods. We refer to the study and observation of the effect of certain drugs and elements on the marrow, now that we have a means of directly observing these effects. We feel that the leukemias present particularly fertile soil for the clinical and research application of this method, and for this reason we have devoted considerable space to the consideration of all the different phases of this field.

THE LEUKEMIAS AND ALLIED CONDITIONS

Present Status of Leukemic Blood Study.—Since 1845, after the independent descriptions of the clinical entity leukemia by Virchow and Bennett, a vast amount of work has established the leukemias on a firm pathologic basis. Theories and classifications have held prominence, to be abandoned later as pathologic knowledge became greater (Virchow's, Banti's, Löwitt's theories). Even during recent years the microchemical methods of blood study (Ehrlich school) have failed not only to differentiate between types of leukemia (myeloid and lymphoid) in certain cases, but have failed in certain types of leukopenic leukemias and primary or secondary aplastic anemias. This necessarily must occur in some cases because blood study is, in reality, a clinical expression of the activity of the bone marrow not necessarily fluctuating as the cellular hyperplasia of the marrow (see aleukemic leukemia).

The work of Schultze [1] and others, regarding the oxydase reaction, has given a clinical method important in the differentiation of lymphoid and myeloid leukemias when such diseases present a leukemic or subleukemic blood picture. Modifications of a granular stain of the Romanowsky type have often failed to differentiate myeloblastic from lymphoblastic cells in their premature state, but with the application of an oxydase method we are furnished with additional evidence which is important in its clinical application. If, however, we accept the marrow origin of the erythroblastic, myeloblastic and lymphoblastic cells from a premature undifferentiated cell (Pappenheim, Maximow, Marchand [2]) then the method may fail if too immature cells circulate in the blood stream.

Present Status of Leukemic Pathology.—With Neumann, in 1870, came a more correct knowledge of the pathologic basis of leukemia, for his dictum that no case of leukemia is on record in which a careful

1. Schultze: Beitr. z. path. Anat. u. z. allg. Path. **45**:127, 1909.
2. Marchand: Verhandl. d. Deutsch. path. Gesellsch. **16**, 1913.

examination has failed to reveal changes in the bone marrow is correct in the majority of cases, although the accumulation of carefully studied material since that date is large.

Walz, Pappenheim and Bradenburg through their investigations arrived at similar conclusions, namely, that the bone marrow in every case of leukemia is the primary seat of the disease and the origin of the cells which give the characteristic microscopic appearance to the blood and that the other organs are only secondarily involved in the general hyperplasia of the lymphadenoid tissue which occurs.[3]

According to Neumann all cases of leukemia can be differentiated by the evidence in the bone marrow. Naegeli, Ziegler, Sternberg [4] and others take exception to this. Naegeli, contrary to the belief of Pappenheim, is not of the opinion that the origin of all lymph cells is from the bone marrow, especially in those cases showing large lymphatic tumors peripherally and only islands of lymphatic tissue in the bone marrow.

Cases of leukosarcoma [4] fall under this category. While the marrow in many cases is infiltrated with lymphatic (?) cells giving a negative oxydase reaction; nevertheless, the intense hyperplasia as noted in the bone marrow in leukemia is not described. Herxheimer [5] believes that leukosarcoma is only a stage of lymphatic leukemia; Paltauf believes the evidence against, while Sternberg adheres to the origin of the tumor masses as being neoplastic in nature and considers the blood picture as an invasion of tumor cells distinct from lymphocytes. Webster,[6] in a review of twenty-six cases, arrives at the conclusion that the disease is not neoplastic in nature but a direct response on the part of the lymphocytes to a chemotactic influence exerted by the disease causing agent, and the infiltration of lymphocytes in the bone marrow is comparable to similar cell accumulations elsewhere in the body.

On the other hand, there are cases of lymphatic leukemia which run their course without clinical or pathological evidence of involvement of lymph glands or other lymphoid tissue. Such a case is reported by Reed [3] and later discussed by Ehrlich. The lymphoid tissue throughout the body was unaffected but the bone marrow was practically entirely composed of lymphocytes. Ehrlich expressed his opinion that such a leukemia might originate from any substratum of lymphoid tissue, such as that in the skin, in the intestinal wall, or in the bone marrow.[7]

Similarly Domarus has described a certain type which has been designated medullary lymphadenoid aleukemia in which the bone

3. Reed: Am. J. M. Sc. **124**:653, 1902.
4. Sternberg: Beitr. z. Path. Anat. u. z. allg. Path. **61**:77, 1916.
5. Herxheimer: Muench. med. Wchnschr. **60**:2506, 1913.
6. Webster: Johns Hopkins Hosp. Bull. **31**:458, 1920.
7. MacCullum: A Textbook of Pathology, Ed. 2. W. B. Saunders, Philadelphia, p. 835.

marrow alone was primarily involved. Recently, in other cases, the same pathology in the bone marrow is described with beginning changes in the lymph glands and spleen.[8] Ghedini in such cases has suggested bone marrow puncture as of diagnostic value. Other cases of acute lymphomatoses run their course under the picture of a hemorrhagic diathesis or a severe anemia without enlargement of lymph glands or spleen.[9] Naegeli,[10] however, is of the opinion that there can be no cases of lymphatic leukemia in which the hyperplasia occurs in the marrow lymphoid tissue alone, but that all the lymphoid tissue is equally involved.

In myeloid leukemia, in addition to hyperplasia of the bone marrow, the anlage of leukopoietic tissue in extramedullary situations usually becomes markedly hyperplastic. A more modern conception[11] seems to be that myelogenous leukemia is not simply a disease of the bone marrow but a disease in which leukopoietic tissue of myeloid type undergoes proliferation all over the body after the removal of some normal inhibitory influence. In contradistinction to lymphatic leukemia, the lymph glands in the myeloid type seldom show myeloid hyperplasia, although such has been noted in the inter-follicular tissue and lymph node follicles in rare instances.[12]

The advocates of diagnostic gland excision for confirmation of either type of leukemia must, at times, tread on uncertain ground. This is less, however, in the lymphatic type, unless there is localized glandular involvement.

It is comparatively simple, in the majority of leukemias, to arrive at a correct diagnosis if such cases present leukemic blood pictures. The value of granular and oxydase stains is questioned as a means of clinical differentiation in some cases. In more recent years, however, we recognize confusing blood pictures in leukemia in certain phases of the disease; one in which the white cells vary in some particular from the usual type encountered, or phases in which the relative numbers of immature white cells remain in essentially the same preponderance but the total count pictures a subleukemic, aleukemic or leukopenic variation. In all blood pictures of leukemia the relative immaturity of the white cells is of vast importance. Contrary to the statement of Pinkus and Ehrlich concerning relative lymphocytosis in lymphatic aleukemia, Hirschfeld states that some cases do not show such and are described as normal.

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8. Hirschfeld: Ergebn. d. Inn. Med. in Kinderh. **7**:164, 1911.
9. Strauch: Med. Rec. **86**:713, 1914.
10. Naegeli: Leukaemia und Pseudoleukaemia. Wien., 1913.
11. Barker: Tr. Ass. Am. Phys. **32**:46, 1917.
12. Citron: Folia haematol. **20**:1, 1915.

Variations of such marked degree may lead to differences of opinion regarding diagnosis. Furthermore, the qualitative blood findings may occasionally fail. This is of decided prognostic importance in dealing with cases of leukopenic leukemia and aplastic anemia. One such case will be reported later. In such variable cases a bone marrow puncture offers opportunity for making a diagnosis. A conclusion based on the pathology of the disease is our most accurate means of diagnosis at the present time, and the cellular content of the long bone marrow is the most constant single pathologic index of either type of leukemia and in any phase of this disease.

Atypical Cases of Leukemia.—In a few cases reviewed from the literature a marrow puncture would have been of decided advantage in arriving at a correct conclusion premortem. Our experience with such cases is small, only two having come under our observation for bone marrow puncture.

Ewald[13] reports the case of a male, aged 37, with six weeks of illness, intense anemia, large spleen, no glandular enlargement. Blood findings: hemoglobin 28 per cent.; red blood cells 740,000, white blood cells 800; differential count: neutrophils, 71 per cent.; large lymphocytes, 2 per cent.; small lymphocytes, 21 per cent.; myelocytes, 3 per cent; transitionals, 3 per cent. Necropsy: Typical picture of leukemia with characteristic changes in the marrow and organs. Marrow smears contained large numbers of typical myelocytes, occasional lymphocyte and occasional nucleated red cell.

Beltz[14] (Case 4): Female, aged 30. Remained in hospital five months until death. On admission: red blood cells, 2,270,000; white cells, 2,500. A later count showed red cells, 1,440,000; white cells, 2,500; the differential count: neutrophils, 10 per cent.; large lymphocytes, 11 per cent.; small lymphocytes, 36 per cent; large mononuclear cells, 10 per cent; myelocytes, none; premature large mononuclears, 34 per cent. Terminally: white cells 101,800, with 78 per cent. premature large mononuclear cells. Necropsy: Long bone marrow brownish red. Microscopically, the most numerous cells were myeloblasts. Findings typical of myeloid leukemia.

Sternberg[15] (Case 1): Female, aged 20. Ten days after vaccination compained of fever, stomatitis and hemorrhages. Examination showed a large spleen and normal liver. Blood count: red cells, 1,950,000; white cells, 3,400; differential count: neutrophils, 12 per cent.; lymphocytes, 87 per cent.; many normoblasts. Blood culture: short chained streptococcus. Necropsy: femur marrow firm and reddish color; smear showed occasional streptococcus, many large lymphocytes and a few small nongranular cells with negative oxydase reaction. A few retroperitoneal lymph glands were enlarged and others on the right side of the neck. Diagnosis: Lymphatic leukemia.

Beltz[14] (Case 9): (Reference is made to this case to show the fallacy of absolute reliance on a bone marrow puncture.) Female, aged 43, died five days after admission to the hospital. Admission blood count: red cells, 1,440,000; white cells, 12,150; 72 per cent. of which were lymphocytes. Two days later: red cells, 1,370,000; white cells, 7,600. Terminally, the whites rose to 27,400. Necropsy: Patches of red cellular marrow in the fatty marrow of the long bones; histologic picture that of myeloid leukemia but definite lymphoid follicles

13. Ewald: Berl. klin. Wchnschr. **43**:870, 1906.
14. Beltz: Deutsch. Arch. f. klin. Med. **113**:116, 1913.
15. Sternberg: Wien. klin. Wchnschr. **26**:553 (June) 1920.

noted in addition. It is easily conceivable that a marrow puncture in this case may have led to incorrect conclusions, depending on whether myeloid, lymphoid or fatty marrow was removed.

The converse of this case, lymphatic aleukemia with stimulation and blood stream invasion of myelocytes, makes a differential diagnosis impossible (Hirschfeld [8]). A marrow puncture in such an instance might lead one astray if such a specimen was isolated from myeloblastic islands.

One might argue in the same manner regarding cases of so-called leukanemia. Following Pappenheim, the lymphatic or myelogenous

Fig. 1.—Smear of bone marrow from a case of myeloid leukemia. Patient, aged 12 years. Specimen diluted with physiologic solution of sodium chlorid. Shows eosinophilic myelocytes and mitotic cells of the white cell series. This patient presented a leukemic blood picture.

overgrowth in the bone marrow is always primary and the megaloblastic and normoblastic activity are explained by the leukopoietic infiltration and crowding out of the red cell elements the remainder of which undergo a compensatory hyperplasia.

One of the first of such cases was described by Leübe and Arneth (quoted from Morawitz [16]).

Male, severe anemia, died during third week. Blood: normoblasts and megaloblasts and a slight increase in the leukocytes, 13 per cent. of which were myelocytes and a few polymorphonuclear cells without granulation. Necropsy: Myeloid metaplasia of the marrow: liver showed no evidences of siderosis.

These few more or less exceptional cases are referred to for completeness. Such cases only exceptionally alter the textbook picture of

16. Morawitz: Deutsch. Arch. f. klin. Med. **88**:493, 1906.

leukemic long bone marrow which is no longer fatty but firm, opaque, yellow gray, pinkish gray or reddish and homogeneous. (Figs. 1 and 6). The hyperplasia is constant in the long bones in both the lymphoid and myeloid type, but we noted less hyperplasia in some cases in the marrow of the tibia as compared with the femur. In the acute leukemias there is practically always a very marked increase of cells in the long bone marrow but not as constant as in the chronic forms. In a few cases only part of the long bone marrow may show infiltration (Naegeli [10]). These cases are classed as exceptional.

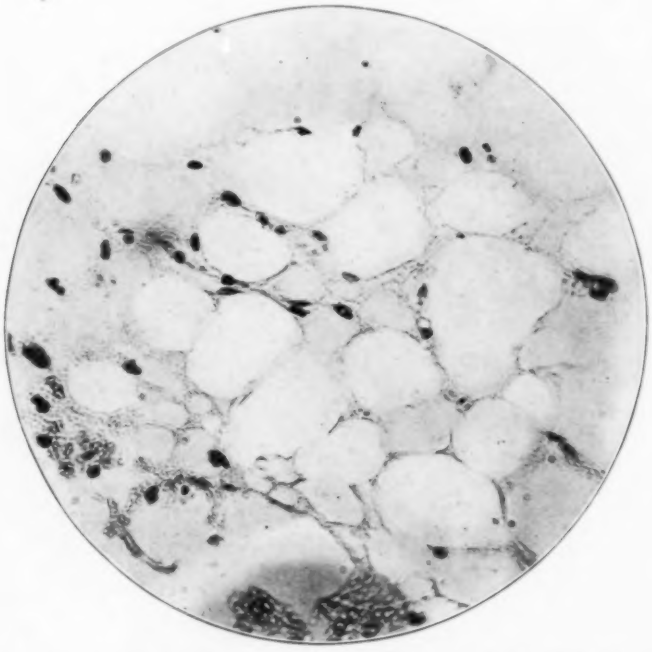

Fig. 2.—Normal adult long bone marrow from the tibia. Subject aged 18 years.

APLASTIC ANEMIAS

The experimental work of Blumenthal and Morawitz (quoted by Kleinschmidt [17]) in regard to aplastic anemias is of interest. They found that in dogs and rabbits repeated blood lettings brought about a disappearance of the erythroblastic and myeloid tissues with abundant increase of the lymphoid elements, that is, changes in the bone marrow which have close connection with those of aplastic anemia in man. The

17. Kleinschmidt: Jahrb. f. Kinderh. **81**:1, 1915.

increase of the lymphoid elements is of paramount importance and their relative increase in a leukopenic blood brings the question of a leukopenic leukemia into the differential diagnosis. On clinical grounds one cannot distinguish all such cases from leukemia. We quote three cases, one of Hirschfeld,[18] one of Engel and Lipowsky and a third of Jagie and Schiffner. It is felt that with such pathology a bone marrow puncture would have been of marked importance in ruling out leukopenic leukemia.

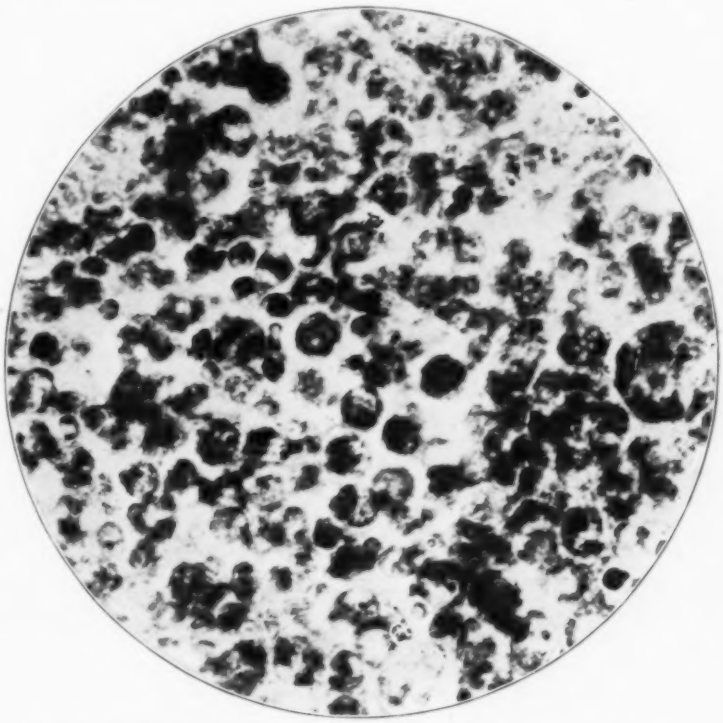

Fig. 3.—Myeloid leukemia. Section taken from bone marrow of femur.

Female, aged 28. Shortly after labor developed progressive anemia with a hemorrhagic diathesis. Disease progressed for four months. Twelve days before death blood count showed: red cells, 1,200,000; white cells, 3,600; 72 per cent. of which were lymphocytes; no normoblasts or megaloblasts. Necropsy: Severe anemia; femur marrow fatty throughout. Ribs—red liquid material showing almost pure lymphocytes, rarely a nucleated red.

Patient entered hospital with hemorrhagic diathesis. Blood count: red blood cells, 2,000,000; hemoglobin, 18 per cent., no nucleated reds and leukopenia; 90

18. Hirschfeld: Berl. klin. Wchnschr. **43**: 545, 1906.

per cent. of white cells were lymphocytes. Death occurred on the eighth day after admission. Necropsy: Yellow fatty marrow in the long bones. Ribs showed many bacteria and were of dirty grayish color.[34]

Female, aged 18. Her illness dated three weeks previously. On entering hospital: bleeding, pallor and enlarged spleen. Blood count: red cells, 2,000,000; white cells, 10,000, 90 per cent. of which were lymphocytes. Shortly before death: red cells, 650,000; white cells, 2,400; hemoglobin, 12 per cent.; differential count: 74 per cent. lymphocytes. Necropsy: No evidences noted of lymphomatosis.[35]

A somewhat similar case of anemia of the aplastic type was one seen by Dr. L. Porter at the Children's Hospital in San Francisco. Through his kindness we punctured the marrow of the tibia and were able to arrive at a correct diagnosis. A synopsis of the case is as follows:

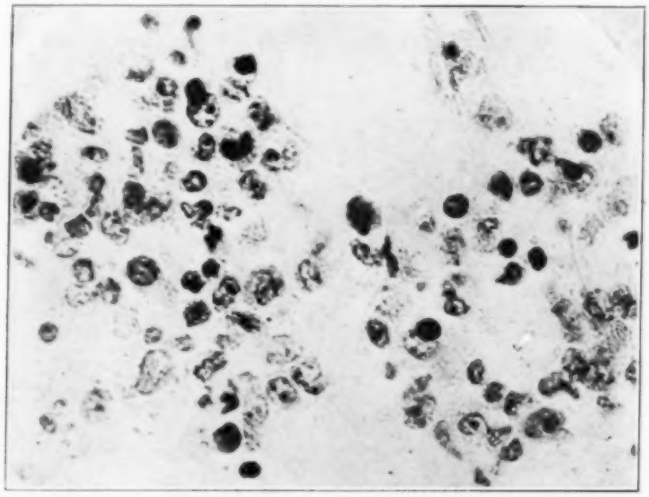

Fig. 4.—Section of bone marrow from femur from a case of sepsis with purpura.

Case 1.—R. J., male, aged 4 years.

Family History.—No hemophilia; mother's sister insane.

Past History.—Full term, 6½ pounds birth weight; normal delivery. Influenza two years ago.

Present Illness.—Child was well until a month ago when he developed fever during the night. Was confined to bed for two days and tired and drowsy afterward. Seventeen days ago again had fever during the night; subsequently progressively got paler. Three days ago had a large hemorrhage from the nose which could not be stopped without packing.

Physical Examination.—Well grown; markedly pale mucous membranes; nares bloody; swollen lips; cervical adenopathy; tonsils small; no stomatitis. Heart and lungs negative, save for a few râles at the bases. Spleen two fingers breadth below left costal margin; liver not enlarged. Skin: No ecchymoses noted. Blood count: Hemoglobin, 32 per cent.; red cells, 1,790,000; white cells, 850; differential count: 1 per cent. neutrophils, 97 per cent. lymphocytes, 2 per cent large mononuclear cells; marked anisocytosis; poikilocytosis; achromia;

platelets reduced; no nucleated reds; many microcytes. The admission temperature was 40 C. Remained elevated for five days and dropped by lysis. All other tests were negative. Marrow puncture on the third day showed an absolutely fatty marrow devoid of marrow cells. No myeloid cells were seen in any of the smears. A few lymphocytes, identical to the type as found in the blood and giving a negative oxydase reaction, were noted in conjunction with normal red blood cells. No blasts or giant cells seen. (For comparison see Figure 6, leukopenic leukemia.)

This marrow picture readily ruled out leukemia and was so decidely aplastic as compared to the long bone marrow in a normal child that a tentative diagnosis of aplastic anemia was made. Cultures from the bone marrow remained sterile. Transfusion of citrated blood and iron was the only means of therapy. The hemorrhages were arrested, the change in blood count was remarkable

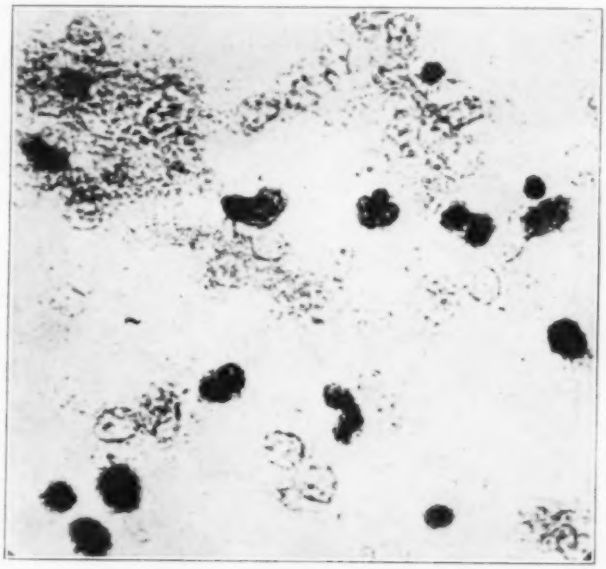

Fig. 5.—Bone marrow from tibia of a case of pernicious anemia. The outlined red blood cells are a constant and unavoidable part of such a postvital preparation. Note the dividing cells of the red cell series.

and the child left the hospital three weeks after admission with much regained strength and a blood count as follows: Hemoglobin, 65 per cent.; white cells, 5,300; neutrophils, 55 per cent.; lymphocytes, 35 per cent.; and 10 per cent. reticulated red cells. A later count, a month after discharge, showed hemoglobin, 62 per cent.; red cells, 3,790,000; white cells, 11,500; color index, 0.81; polymorphnuclear neutrophils, 60 per cent.; eosinophils, 1 per cent.; large lymphocytes, none; small lymphocytes, 28 per cent.; large mononuclears, 6 per cent.; myelocytes, 5 per cent. Both macrocytes and microcytes present with moderate poikilocytosis. Reticulated reds, about 3 per cent. The child continued to improve temporarily, relapsed and died in the second month of its illness. No postmortem was done.

ETIOLOGY OF THE LEUKEMIAS

Before concluding this brief résumé on the subject of leukemias, the etiology of the disease might well be considered. Briefly stated, tumor formation (Banti) or an abnormal response of the myeloid or lymphoid tissue to recent or latent infections are points much discussed. Advocates of an infectious etiology include such men as Hertz, Pappenheim, Pawlowsky, A. Fraenkel, Ziegler, Jockman, Wilbur and Sternberg.

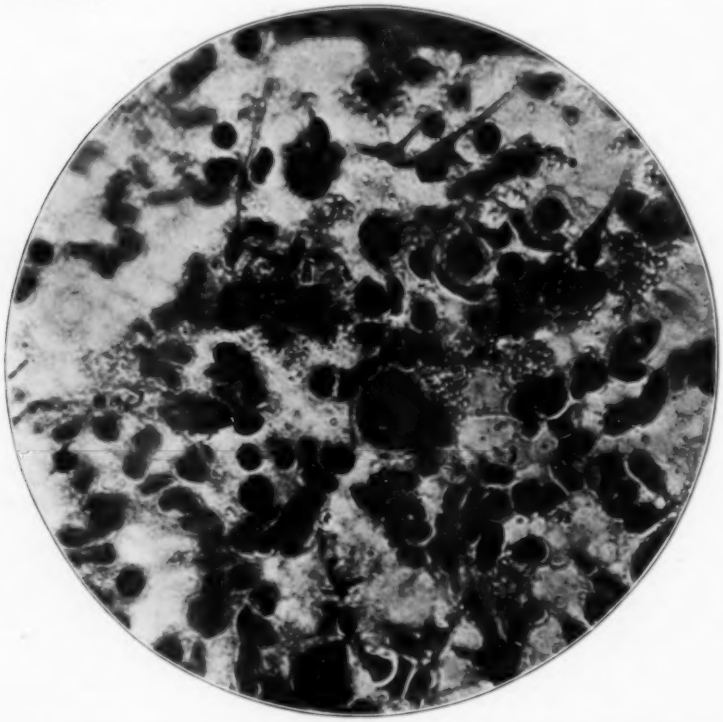

Fig. 6.—Bone marrow smear taken from tibia in a case of myeloid leukemia. Myeloblasts, myelocytes, nucleated red cells and undifferentiated cells (stem cells) are seen. This patient presented a leukopenic blood picture and the diagnosis was made from the marrow smear. The patient was 9 years of age.

That the clinical picture of acute leukemia with temperature elevation, stomatitis, purpura, hemorrhage, anemia and glandular and splenic enlargement constitutes a group which parallels certain of the severe septic states is not doubted. Furthermore, the termination of many of the chronic forms of leukemia may present a similar picture. To such an extent is this true that very recently Sternberg [15] stated as his belief

that acute leukemias do not exist as an entity but are all on a chronic basis. It is thus important, following Naegeli, to know whether or not the blood count was normal previous to an acute leukemia.

Various types of organisms have been described as occurring in the blood or tissues, the seat of leukemic changes. In a far greater proportion of cases no etiology is forthcoming. Sternberg,[19] after isolating a diplostreptococcus from some of his cases, was unable to produce leukemic pathology in rabbits. (He likewise failed with staphylococcus and pneumococcus.) Pappenheim, Naegeli and Hirschfeld emphasize the fact that the blood pictures in some cases of general bacterial infection are identical with those of acute myeloid leukemia, the only difference being the issue. These changes probably represent a biologic reaction of the hemopoietic system to various nonspecific, generally septic infections which, as a rule, call forth a leukocytosis, under certain circumstances, however, a myelocytosis.

Cases reported by Cabot,[20] Jackson and Smith,[21] Türk and Lüdke (quoted by Sternberg[15]) are quoted as infectious states presenting leukemic blood pictures with recovery. Even mechanical irritation of the bone marrow (multiple fractures of leg—Simon[22]) has given rise to a leukemic blood picture. Other cases of infectious disease with many premature white cells in the blood, but death occurring from the disease per se, are noted (Stevens[23]). We have recently seen a child of 12 with a well advanced empyema of the left chest cavity (streptococcus) and 48 per cent. myelocytes in the blood smear.

After severe infections which normally call forth a high leukocytosis (pneumonia for example) it is not uncommon after the crises to find from 4 to 5 per cent. myelocytes in the blood. In children this is more common and in infants under 1 year; according to Rotch and Morse,[24] the presence of myelocytes in sick children is without significance. Histologically, one finds at this age the long bone marrow richer in cellular content than the sparsely cellular fatty long bone marrow of the adult, the marrow of the ribs in older individuals giving origin to practically all the red and white cells (Fig. 2).

Wherein lies the difference in the fatal prognosis of the leukemias and the questionable outcome of septic states with leukemic blood pictures? Is it because in leukemia the marrow proliferation is due to a disturbance of the mechanism governing cell production rather than a response to chemiotaxis in the ordinary sense? In this connection it is

19. Sternberg: Wien. klin. Wchnschr. **24**:1623, 1911.
20. Cabot: Osler and McCrae, Modern Medicine, **4**:676.
21. Jackson and Smith: Boston M. & S. J. **172**:136, 1915.
22. Simon: Am. J. M. Sc. **132**:144, 1906.
23. Stevens: Lancet **2**:791, 1902.
24. Rotch and Morse: Boston M. & S. J. **152**:729, 1905.

not an uncommon clinical observation to observe in patients with myeloid leukemia suffering with intercurrent infections, an aleukemic or subleukemic blood picture and diminution in the size of the spleen. We recently observed a patient with myeloid leukemia suffering from pneumonia with a blood count comparable in all respects with the leukocytosis of the disease and with a relative diminution in the size of the spleen to the extent that during observation of the pneumococcus infection leukemia was not suspected by the attending physician. During the postconvalescent stage, however, the blood picture again became leukemic and the spleen increased markedly in size.

The pathologic differentiation between bone marrow hyperplasia in continued septic states and that of myeloid leukemia is at times difficult. The most outstanding feature is the degree of hyperplasia of the marrow (Figs. 3 and 4).

"Only by further bacteriologic and perhaps protozoologic studies of the blood, bone marrow, spleen and lymph glands of such patients and by animal inoculation from the tissues involved including bone marrow trephined from the living bone can we clarify the problem." Following Wilbur's [25] quoted suggestion regarding the etiology of acute leukemia, marrow cultures were taken from two persons trephined during life and the material subjected to the ordinary cultural methods. Each failed to show any bacteriologic growth. This evidence is decidedly inconclusive; the work is to continue when opportunity presents.

We are well aware of the work of Ward [26] and his arguments and conclusions against the infectious origin of the leukemias. At present we offer nothing in refutation.

In conclusion, we must leave the field of leukemias as reviewed. We have drawn from the literature certain atypical cases, the diagnoses of which might have been made more certain by marrow puncture. Such a series must of necessity be grouped from reports, as individual experience in a single clinic does not cover such a field.

PRIMARY ANEMIA, SECONDARY ANEMIA, POLYCYTHEMIA

The question of the value of "intravitam" bone marrow studies in pernicious anemia was approached with a conservative state of mind, as we felt that such studies would throw no light on the etiology of the disease. We assume bone marrow changes, in pernicious anemia, as being secondary to the causal factor or factors, but we believe it is important in both diagnosis and prognosis to determine what is taking place in the bone marrow. Such study will improve our diagnostic criteria and serve to separate, at an earlier period, those anemias with

25. Wilbur: J. A. M. A. **65**:1255 (Oct. 9) 1915.
26. Ward: Brit. J. Child. Dis. **14**:10, 1917.

a clinical picture of pernicious anemia but due to sepsis, syphilis, malaria, recurrent hemorrhages, carcinoma of the stomach, carcinoma and sarcoma involving bone marrow, anemias due to intestinal parasites, etc., etc.

That the need of such studies is felt may be inferred from the statement by Minot [27]: "The pathology of the bone marrow has not been studied as one might wish. Future studies may decide whether or not there is any absolutely distinctive feature of it that is associated only with pernicious anemia."

The phase of this disease in which bone marrow studies will probably be of most value is prognosis. Our prognostic criteria at present are dependent largely on blood studies, it being assumed that at any given period the pathologic elements in the peripheral circulation are an index of what is occurring in the bone marrow. Experimental work in animals, in part, bears this out, notably the work of Bunting,[28] who, by injecting ricin into rabbits, was able to reproduce the marrow picture of pernicious anemia. The following quotation elucidates this point:

> Applying these conclusions to pernicious anemia, it seems possible that an analagous (to ricin) toxin may be present destroying red cells both in the circulation and in the marrow so that in the reaction nucleated red cells are used to supply the deficiency—that further action of the toxin reduces the erythrogenetic groups more or less to the megaloblastic centers, diminishing greatly the regenerating power of the marrow and resulting in a discharge of megaloblastic cells in the hasty effort to supply the needs of the circulation. Thus the regular orderly development of the groups of the marrow cells is interfered with and a short cut is taken from the megaloblast to the macrocyte, an imperfect immature cell, as shown by its polychromatophilia and granular basophilia. In this light it is not difficult to see why cases of pernicious anemia with few normoblasts and more megaloblasts in the circulation are of graver prognosis than those with a large number of normoblasts and few megaloblasts, and, again, if one regards the presence of nucleated cells in the circulation as evidence of injury to the bone marrow, one has an explanation for the "nucleated red cells crises" of pernicious anemia and leukemia in which the blood picture resembles much that is shown in ricin intoxication.

These observations and deductions seem to Bunting to offer "a not unsatisfactory explanation of the so-called reversion of the marrow to the embryonic type in pernicious anemia."

It has been well established that at times, and in certain stages of the disease, critical blood studies give fairly satisfactory information as to what is occurring in the bone marrow. Our marrow punctures in pernicious anemia, up to date, have not yielded much information in addition to that gained from a careful study of the history of the case and careful blood studies. This was due, in great part, to the type of case selected. We have performed marrow puncture in five cases of

27. Minot: Oxford Medicine **2**, 1920.
28. Bunting: Johns Hopkins Hosp. Bull. **36**:222, 1905.

pernicious anemia. In one case three punctures were made, in another case two punctures were made, making eight punctures in all. Three of these cases showed a red marrow with few cells and no signs of division. These three cases were of long standing and had been in a state of relapse for several months. Two patients survived the last puncture only about six weeks; one lived for about three months after examination of the marrow. One case presented a pinkish grey marrow, with a moderate amount of cellular activity and very few megaloblasts. Subsequent study and observation of the case cast some doubt on the accuracy of the diagnosis of pernicious anemia. These three cases with inactive marrows would seem to belong to the class of case termed by Minot and Lee [29] the myelotoxic type. This type of case is undoubtedly the least promising for bone marrow study.

In the earlier types of cases if the ratio between blood destruction and cell regeneration can be estimated a fairly definite prognosis can be made. Various methods have been devised to estimate hemolysis or blood destruction. Bone marrow studies will give a fairly accurate conception of the phase of regeneration. One of our patients, a male, aged 40, a laborer, belonged to the earlier type of case. He had had two very satisfactory remissions in two and one-half years since the onset of his illness. During these remissions he was able to earn his livelihood by manual labor. During the two weeks in hospital before we saw him he had an intermittent temperature, from one to two degrees above normal. He had urobilin in the urine and showed signs of hemolysis. His red cells numbered less than two million with a high color index and the blood smears showed a moderate number of regenerative forms. The marrow smears showed a red marrow with abundant signs of cellular activity. In Figure 5 some of these cells are shown. We felt that this man would have a satisfactory remission. He left the hospital in about three weeks very much improved. We believe that in this case the marrow gave somewhat more accurate information than blood studies had furnished.

In certain atypical cases, marrow studies will probably be of considerable practical importance. For example, Ellermann [30] has been impressed in his studies on the histology of pernicious anemia by the presence in certain cases of considerable numbers of myelocytes in the marrow and in the liver and spleen. He mentions myelocytes as being plentiful in the marrow in every instance in his series of twelve cases studied postmortem. Minot [27] mentions the fact that there are cases in which a great outpouring of immature white cells and blasts occurs, the white count in some cases reaching as high as 50,000, causing an incorrect diagnosis of leukemia to be made.

29. Minot and Lee: Boston M. & S. J. **177**:761, 1917.
30. Ellermann: Acta Med. Scandinavica **53**:718, 1919.

The whole picture is much more sharply defined in these cases if one knows what is occurring in the bone marrow.

There are other hemolytic and septic anemias in which bone marrow studies may yield information of practical value. We have studied the marrow postmortem in a case of sepsis with severe hemorrhage (Fig. 4). The protocol at necropsy stated that clinically the patient had an aplastic bone marrow, as no regeneration forms were found in the blood. Bone marrow from the femur, sectioned and studied microscopically, shows a remarkable picture of activity. One or more transfusions in this case might have turned the balance in favor of the patient.

It has occurred to us in connection with bone marrow studies in pernicious anemia and other anemias that certain vital staining methods, such as employed by Evans[31] in vital staining of endothelial leukocytes might yield information of value in determining the origin of the different types of cells found in the marrow. Such studies are in progress, as well as staining work to determine the presence or absence of deposits of hemosiderin in the marrow in pernicious anemia.

At this point it may be well to call attention to the fact that we do not advocate bone marrow puncture in pernicious and other anemias as a method to supplant blood studies, but merely as an additional source of information in selected cases.

Another field of some promise for the application of marrow puncture is that of the polycythemias. It is usually possible clinically to separate polycythemia vera with splenomegaly from symptomatic polycythemia. It will be possible to collect data in the former type of case bearing on the question of whether, as suggested by some,[32] the bone marrow is the site of the disease. This is a question of some importance as other investigators, notably Blumenthal,[33] report cases in which a necropsy was performed and a fatty bone marrow was found showing no alterations. We have investigated one case of over two years' duration with red cell counts reaching as high as 12,000,000. This patient had a left-sided hemiplegia resulting from a cerebral hemorrhage and also a rather large hemorrhage into the orbit on one side. There was no demonstrable enlargement of the spleen. Marrow puncture in this case showed a fatty marrow with no evidence of cellular activity. The whole question of bone marrow findings in polycythemia is in need of further study and perhaps revision.

DISCUSSION

It has been our purpose in this preliminary note to present the method, establish its feasibility and outline its scope of usefulness.

31. Evans: Anat. Rec. **8**:98, 99, 1914.
32. Weber & Watson: Internat. Clin. **4**:47, 1905.
33. Blumenthal: Bull. de l'Acad. Roy. de méd. de Belgique, Ser. 19, 1905-4.

There are certain phases of bone marrow study, certain possibilities that we have had in mind but have not touched on in this paper. We have no data and the considerations are, therefore, purely theoretical. We refer to bone marrow cultures in septic anemias and in generalized sepsis in which organisms are not always present in the peripheral circulation. Chronic and subacute endocarditis may be taken as a type example. Certain cases of chronic malaria in which no plasmodia can be demonstrated in the peripheral circulation may yield plasmodia in bone marrow smears. We have such a case under investigation now. Clinically, the patient presents an enlarged spleen with a leukopenia and an anemia. There is a past history of syphilis and of malaria. The possibilities for the employment of the method are many but it may be argued that it is too dangerous and too much of a surgical procedure to be practical. We believe that with ordinary care and asepsis in technic the danger of infection is very slight. With the use of local anesthesia to the skin and periosteum the patients do not complain of pain and discomfort. It is hoped that in centers where material is available for study, the method will be employed and data collected to determine whether or not it deserves a place among recognized procedures for clinical investigation.

THE BASAL METABOLISM IN NONTOXIC GOITER AND IN BORDERLINE THYROID CASES

WITH PARTICULAR REFERENCE TO ITS BEARING IN DIFFERENTIAL DIAGNOSIS *

JAMES H. MEANS, M.D., AND HARRIET W. BURGESS, A.B.
BOSTON

An extended study of the basal metabolism in its relation to the clinical features of toxic goiter [1] has been in progress in this clinic since June, 1914. As a by-product of this work there has been collected a considerable amount of data on patients with clinically nontoxic goiter and on patients without frank hyperthyroidism or hypothyroidism, but in whom the possibility of one of these conditions was suspected, and also on patients with a variety of pathologic states not including the thyroid. Since the use of the basal metabolism determination as a test of thyroid function has come into rather wide use in the last two or three years, it has seemed to us advisable to place these data on record. A large amount of data on normal persons, which, as regards the thyroid problem, serves as normal control data, has been secured by Benedict of his associates.[2] Our own data presented here are in the nature of pathologic controls.

Between June 10, 1914, and Oct. 22, 1921, one thousand patients were observed in the metabolism laboratory at the Massachusetts General Hospital, and on these, 2049 determinations were made. The methods used have been discussed in previous papers. The Benedict apparatus has been used from the beginning—until July, 1921, the universal type,[3] since then the portable.[4] Up to May, 1917, we determined both carbon dioxid and oxygen, and made the calculation of heat produc-

* From the Medical and Surgical Services of the Massachusetts General Hospital, aided, in part, by a gift from Dr. William Norton Bullard.

1. Means, J. H.: Basal Metabolism and Body Surface, J. Biol. Chem. **21**: 263, 1915. Studies of the Basal Metabolism in Disease and Their Importance in Clinical Medicine, Boston M. & S. J. **174**:864, 1916. Hyperthyroidism: Toxic Goiter, M. Clin. N. America **3**:1077, 1920. Determination of the Basal Metabolism as a Method of Diagnosis and a Guide to Treatment, J. A. M. A. **77**:347 (July 30) 1921. Means, J. H., and Aub, J. C.: Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, J. A. M. A. **69**:33 (July 7) 1917. Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**:645 (Nov.) 1919.

2. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Carnegie Inst. Washington, Pub. 279, 1919.

3. Benedict, F. G.: Ein Universalrespirationsapparat, Deutsch. Arch. f. klin. Med. **107**:160, 1912.

4. Benedict, F. G., and Collins, W. E.: A Clinical Apparatus for Measuring Basal Metabolism, Boston M. & S. J. **183**:449, 1920.

tion from the respiratory quoteint obtained. Since then we have determined oxygen only and used an assumed respiratory quotient of 0.82. The Sage Institute standards have been used in determining variations from the normal.[5] For the purpose used we believe the above procedure is sufficiently exact. For certain problems in metabolism it might not be. The Benedict apparatus, despite various criticisms in the literature, has proved highly satisfactory in our hands. Boothby and Sandiford[6] have suggested that it is not sanitary. We have never seen evidence to substantiate this, and we should like to point out that with the latest type of apparatus there is no chance for infection.[4] The possible sources of infection are the mouthpiece itself, water of condensation in the tubing, and the air contained in the apparatus. The mouthpiece, of course, is always sterilized by everyone. Water of condensation that might run back from piping to patient, in the portable Benedict is found solely in the F shaped metal member to which the mouthpiece is attached. We have adopted the custom of always boiling this metal member with the mouthpiece, and recommend this practice to others. The air is entirely refreshed between patients by raising and lowering the spirometer bell several times.

In our series of one thousand cases there are included most of those cases of disturbed thyroid function that have come to the hospital during the period covered, for it has become a routine to follow the basal metabolism of patients being treated for hyperthyroidism or hypothyroidism. We also have a group of borderline thyroid cases in which the metabolism was determined as an aid in differential diagnosis, a series of patients with blood diseases, various endocrine diseases other than those of thyroid origin, and a group of miscellaneous nonendocrine conditions. These 1,000 cases were distributed as follows: Clinically thyrotoxic, 300 cases; clinically myxedema and cretinism, 32 cases; goiters clinically nontoxic, 102 cases; borderline cases in which hyperthyroidism was suspected, 290 cases; borderline cases in which hypothyroidism was suspected, 70 cases; other endocrine diseases, 41 cases; blood diseases (anemia, leukemia and polycythemia), 66 cases; miscellaneous nonendocrine diseases, 99 cases.

It is our purpose at the present time to discuss these cases only in so far as they bear on the question of the value of the determination of the basal metabolism in the diagnosis of thyroid activity. Certain of the groups will be discussed in detail in later papers.

Subnormal Metabolism.—We first studied the occurrence of subnormal metabolism. This is generally considered one of the cardinal

5. Aub, J. C., and DuBois, E. F.: Clinical Calorimetry; Nineteenth Paper. The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (June) 1917.

6. Boothby, W. M., and Sandiford, I.: Basal Metabolic Rate Determinations, Philadelphia, W. B. Saunders Co., 1920.

laboratory signs of myxedema and cretinism. Of the thirty-two cases of these diseases there were twenty-six which had received no thyroid. All of these twenty-six cases showed a reduction below minus 10 per cent. in the metabolic rate. The average findings in the several types included in this group are shown in Table 1.

TABLE 1.—BASAL METABOLISM IN MYXEDEMA AND CRETINISM

Type	Number of Cases	Average Basal Metabolic Rate, Per Cent.
Spontaneous myxedema	16	—25
Roentgen ray myxedema	4	—21
Cachexia strumipriva	2	—17
Cretinism	4	—19

This finding, namely, that a low metabolism occurs in 100 per cent. of the untreated cases which show the clinical picture of myxedema or cretinism, would seem to prove that a low metabolism is an essential feature of those diseases.

We next looked into the occurrence of subnormal metabolism in conditions other than frank myxedema and cretinism. After excluding these conditions, there were found to be sixty-three cases with basal metabolic rates of — 11 per cent. or lower. The degree of reduction, and the relative number occurring in each group, are shown in Table 2.

TABLE 2.—OCCURRENCE OF SUBNORMAL METABOLISM

Basal Metabolic Rate, Per Cent. (Inclusive)	Group: Number of Cases							Per Cent.
	Suspected Hyperthyroidism	Nontoxic Goiter	Miscellaneous Nonendocrine	Suspected Hypothyroidism	Other Endocrines	Blood Diseases	Total All Groups	
—11 to —12	5	3	5	8	3	1	25	40
—13 to —14	3	2	2	3	3	0	13	20.5
—15 to —16	2	1	1	2	7	0	13	20.5
—17 to —18	1	0	0	0	3	0	4	6.5
—19 to —20	0	0	0	0	1	0	1	1.5
—21 or less	1	0	0	2	3	1	7	11
Total with subnormal rates	12	6	8	15	20	2	63	100.0
Total cases in group	290	102	99	70	41	66	668	
Per cent. of group with subnormal rates	4.1	5.9	8.1	21.4	48.8	3.0	9.3	

This table shows that subnormal metabolism in diseases other than those of the endocrine glands is distinctly infrequent. Of the sixty-three cases studied, fifty-three, or 84 per cent., were either definitely endocrine or presented some clinical suggestion of endocrine disease. Furthermore, of the ten nonendocrine cases, eight showed rates between — 11 and — 14 per cent., hence their degree of subnormality was

slight. Also, grouping endocrine and nonendocrine cases together, 81 per cent. of all the cases have rates between — 11 and — 16 per cent., which is higher than any of the myxedema averages.

The group of endocrine diseases other than thyroid includes suprarenal and pituitary abnormalities, and it is known that in hypopituitarism there sometimes is a reduction in the basal metabolism.[7] There seems also to be one in Addison's disease.[8] The group of blood cases shows that in anemia, polycythemia and leukemia, subnormal metabolism is a distinct rarity.

Supernormal Metabolism.—In a similar way we studied the occurrence of supernormal metabolism. Of the 300 cases showing definite clinical signs and symptoms of hyperthyroidism (except in certain instances after operation or roentgen-ray treatment) there was but one case (0.3 per cent.) which failed to show a metabolic rate of more than +10 per cent., and that patient had very mild symptoms.

The occurrence of supernormal metabolism in the remaining cases is shown in Table 3.

TABLE 3.—Occurrence of Supernormal Metabolism

Basal Metabolic Rate, Per Cent. (Inclusive)	Group: Number of Cases							Per Cent.
	Nontoxic Goiter	Suspected Hypothyroidism	Miscellaneous Nonendocrine	Other Endocrines	Suspected Hyperthyroidism	Blood Diseases	Total All Groups	
+61 to +90	0	0	0	0	0	2	2	1
+41 to +60	0	0	0	0	6	10	16	8
+26 to +40	0	1	2	1	17	9	30	15
+19 to +25	0	3	5	3	22	10	43	21
+15 to +18	1	2	5	1	27	8	44	22
+11 to +14	12	3	8	5	33	6	67	33
Total with supernormal rates	13	9	20	10	105	45	202	100
Total cases in group	102	70	99	41	290	66	668	
Per cent. of group with supernormal rates	12.7	12.9	20.2	24.4	36.2	68.1	30.2	

Aside from clinical hyperthyroidism, the greatest incidence of supernormal metabolism is in the group of blood diseases. This is consistent with the findings of several observers that there is practically always an increase in leukemia[9] and not infrequently in the severe

7. Boothby, W. M.: The Basal Metabolic Rate in Hyperthyroidism, J. A. M. A. **77**:252 (July 23), 1921.

8. Aub, J. C.: An unpublished research.

9. The literature on this point is summarized by Murphy, J. B.; Means, J. H., and Aub, J. C.: Clinical Calorimetry; Twenty-third Paper. The Effect of the Roentgen Ray and Radium Therapy on the Metabolism of a Patient with Lymphatic Leukemia, Arch. Int. Med. **19**:890 (June) 1917. See also Gunderson, A. H.: The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, Boston M. & S. J. **185**:785, 1921.

anemias.[10] The group showing the next greatest incidence is that of cases not presenting the full clinical picture of hyperthyroidism, but some suggestion of that condition. This is not surprising. Of the other endocrine 24.4 per cent. show slight elevations.

The twenty cases (20.2 per cent.) out of ninety-nine in the miscellaneous nonendocrine group need some comment. There were two cases each with a rate of + 26 per cent. (none higher). One of these patients was a woman seven months pregnant. When seen four months later during lactation the rate was + 13 per cent. The other patient with a rate of + 26 per cent. did not keep absolutely quiet during the test. One patient with a rate of + 23 per cent. had malignant lymphoma of the neck. Two weeks later after vigorous roentgen-ray treatment her rate was + 14 per cent. Another patient with a + 23 per cent. rate had paralysis agitans. It was thought that the tremor might well explain this elevation, as a week later when he was quieter it was —2 per cent. Rates of + 21 per cent. were found in a case of osteitis deformans and in one of questionable chlorosis. A second test on this patient three months after the first test showed a rate of +14 per cent. In one case of paroxysmal tachycardia during the paroxysm there was a rate of + 20 per cent. The remaining thirteen cases had rates not higher than + 18 per cent. Their supernormality, therefore, was slight.

Nontoxic Goiter.—Coming now to the group of 102 clinically nontoxic goiter cases, the average basal metabolism rate was: with regard to sign, + 2 per cent., and without regard to sign, ± 6.4 per cent. As we have pointed out elsewhere,[11] in making averages of this sort the average with regard to sign indicates whether there is a positive or negative bias in the series (in this instance a very slight positive one), and the average without regard to sign, the general degree of normality of the series, as shown by the prevailing magnitude of the variations. This series of nontoxic goiters from the metabolism point of view shows a very high grade of normality. It compares in that respect very favorably with a group of thirty-one normal men studied by Carpenter et al.[2] This latter group showed average rates as follows: with regard to sign, —1.7 per cent.; without regard to sign, ± 5.1 per cent.

A result such as this in nontoxic goiter makes one wonder whether the thirteen of these 102 cases that showed rates greater than + 10 per

10. Meyer, A. L., and DuBois, E. F.: The Basal Metabolism in Pernicious Anemia. Clinical Calorimetry, No. 15, Arch. Int. Med. **17**:965 (June), 1916. Tompkins, E. H., Brittingham, H. H., and Drinker, C. K.: The Basal Metabolism in Anemia, with Especial Reference to the Effect of Blood Transfusion on the Metabolism in Pernicious Anemia, Arch. Int. Med. **23**:441 (April), 1919.

11. Means, J. H., and Woodwell, M. N.: Remarks on Standards for Normal Basal Metabolism, Arch. Int. Med. **27**:608 (May) 1921.

cent., or the six that were lower than —10 per cent., were not really suffering from either a mild grade of hyperthyroidism in the first instance or of hypothyroidism in the second instance.

We searched further, to see whether the different types of nontoxic goiter showed any constant tendencies, but without finding any such. The series was divided into several subgroups, and the average rates obtained are shown in Table 4.

TABLE 4.—Nontoxic Goiter

Type	Number of Cases	Metabolism Variation With Regard to Sign, per Cent.	Metabolism Variation Without Regard to Sign, per Cent.
Adenomata	38	+2.7	±6.9
Cystic	11	+1.2	±5.0
Diffuse enlargements	37	+1.1	±6.3
Diffuse enlargements in adolescents	16	+2.1	±7.1

There was no conspicuous tendency for the cases showing subnormal or supernormal rates to fall exclusively into any of these subgroups.

Suspected Hypothyroidism.—The average figures for the group of seventy patients who clinically were suspected of having hypothyroidism, but in whom the entire picture of frank myxedema was lacking, were: with regard to sign, —1.4 per cent.; without regard to sign, ± 8.7 per cent.

The negative bias here is slighter than the positive bias in the previous group, but there is a larger proportion of cases with abnormal metabolism. Nine, for example, show rates of + 11 per cent. or higher, and fifteen show rates of — 11 per cent. or lower. A certain number of low rates we should expect, but the high ones are, perhaps, a little surprising, but if we examine them closely we can in several instances find adequate explanations. For instance, one case with a rate of + 26 per cent. had some signs suggesting myxedema, but others suggesting acromegaly. A second with a rate of + 24 per cent. had a picture suggesting myxedema, but was taking large doses of thyroid at the time the test was made. A similar explanation can be found for one of the cases showing a rate of + 15 per cent.

Suspected Hyperthyroidism.—The last group, that of cases suspected for some clinical reason—nervousness, tachycardia, or other such manifestation—of having hyperthyroidism, showed, as is not surprising, a somewhat greater variation. There were 290 cases in this group, and the average rates were: with regard to sign, + 7.1 per cent.; without regard to sign, ± 10.2 per cent.

Here there is a somewhat greater bias (positive) than we have met before, but still it is not so very large. The individual variations too tend to be larger than in the previous two groups. For example, there are 105, or 36 per cent., which show rates higher than + 10 per cent., and twelve, or 4 per cent., with rates lower than —10 per cent. A survey of the twelve with subnormal metabolism shows that they were all cases in whom the suggestion of hyperthyroidism was very slight. They were a type in which hyperthyroidism was a possibility in the mind of the clinician rather than a probability, and the metabolism test was made for exclusion only. Coming now to the 105 with supernormal metabolism we find that forty-four of them have rates between + 11 per cent. and +16 per cent., sixty between + 11 per cent. and + 18 per cent., and eighty-two between + 11 per cent. and + 25 per cent. Seventy-eight per cent., therefore, showed elevations of a slight grade only. A further investigation shows that of the 105 cases, seventy-five, or 71 per cent., had but one metabolism test performed. An analysis of these 105 cases, case by case, is hardly worth while. A considerable proportion of them very likely really were suffering from hyperthyroidism. The rest were cases of psychoneurosis, effort syndrome, organic heart disease, in which because of nervousness or tachycardia or some such sign the clinician wished to exclude thyrotoxicosis. Of the thirty cases in which more than one test was made, there were ten in which a second test was performed within a fortnight after the first. In each case the second test was lower, the average of the first tests being + 37 per cent., and of the second + 18 per cent.

DISCUSSION

Our object here has been to shed light on the merit of the determination of the basal metabolism as a functional test of the thyroid. On this problem, of course, only indirect evidence can be had from human beings. Our findings, however, in nontoxic goiter and borderline thyroid cases, added to those already recorded in the literature, we believe furnish some indirect evidence of value.

In the first place, it seems clear that in untreated myxedema and cretinism there is invariably a subnormal metabolism, the average rate in our twenty-six cases being — 23 per cent. After treatment with thyroid the rate rises toward normal.

In the second place, in patients showing definite clinical signs of hyperthyroidism there is invariably a supernormal metabolism, and as has been shown elsewhere, the degree of elevation runs roughly parallel to the intensity of the symptoms and signs.[1]

Of course, it may justly be said that to consider metabolic rates varying more than 10 per cent. above or below the standard abnormal,

and those that vary less than 10 per cent. not abnormal, is an entirely arbitrary procedure. It is arbitrary but, nevertheless, reasonable. A line must be drawn somewhere for purposes of analysis. This 10 per cent. limitation covers the known facts very satisfactorily, therefore, its use serves a good purpose. But in interpreting the significance of basal metabolic rates in patients it must be borne in mind that there is no absolute line of demarcation between normal and abnormal metabolism. We should have no hesitancy in saying that a rate of + 80 per cent. (provided there was no technical error), or one of —25 per cent., was pathologic, but we could not say so with certainty in regard to one of + 16 per cent. or —14 per cent.

A certain number of patients with other kinds of endocrine disease, pituitary, suprarenal, etc., show subnormal metabolism, but in persons without clinical evidence of endocrine disease, subnormal metabolism is distinctly uncommon, and when it does occur the degree of depression is slight as compared with frank myxedema and cretinism.

Supernormal metabolism in conditions other than clinical thyrotoxicosis is more frequent. It nearly invariably occurs in leukemia, and often in the severe anemias and polycythemias. Except in the group of blood diseases, the elevation is generally slight as compared with toxic goiter. It should be pointed out that fever is often accompanied by an elevation of the basal metabolism, but the present analysis is based on afebrile patients.

Our series of 102 patients with goiter, but without clinical signs or symptoms of hyperthyroidism or hypothyroidism, shows nearly as high a grade of normality as does Carpenter's series of normal men. Our average for the group was + 2.04 per cent. It is also interesting to note that Boothby [7] with an entirely different technic got an average of + 2 per cent. in a series of 254 similar cases.

In other words, in clinical hyperthyroidism we find increased metabolism, in clinical hypothyroidism decreased metabolism, and in goiter clinically nontoxic we find an essentially normal metabolism. One might ask, therefore, whether the determination of the metabolic rate added anything to our knowledge of such cases. Perhaps it does not, in so far as diagnosis is concerned, except to add a quantitative impression of the severity of the disease which is of distinct help in following its course and the effect of treatment. It is in the borderline group of cases, that is to say, those cases with symptoms or signs that suggest the possibility of abnormal thyroid function, that the metabolic rate determination really helps in diagnosis.

Our group of cases of suspected hypothyroidism, on the whole, shows a high grade of normality of metabolic rate, and of the patients that did have subnormal rates several showed improvement in symptoms

on being given thyroid. In the group of suspected hyperthyroidism cases there is a higher incidence of abnormal metabolism, but even here two thirds of the cases were within the normal range. Whether the remaining third showing supernormal rates were really thyrotoxic we cannot say. We feel that probably many of them were, their clinical pictures being highly suggestive.

We must point out that with many of our patients (that is to say, in those where the test was made for diagnostic purposes) a single test only was performed. There is no doubt that the first test in certain subjects, particularly those at all alarmed by the procedure, does not give a true basal value. The work of Aub and his associates [12] suggests that this may be due to an increased flow of epinephrin. In doubtful cases second, and if necessary third tests (on different days) should be made. When errors occur, however, they are always in the direction of giving too high values. Leaks in the apparatus, restlessness or alarm on the patient's part, all tend to increase the observed metabolism.

We feel, therefore, that the finding of normal rates in persons suspected of having hyperthyroidism practically rules that condition out, but the finding of an elevated rate does not necessarily rule it in. The safest procedure and one which we carry out wherever possible is, on finding an elevation in rate in a person with questionable clinical picture, to repeat the test, until a constant reading on different days is obtained. When a base line for the given patient is reached, then the interpretation may be made. In our experience, however, it is extraordinary what a large proportion of patients show normal rates on the first observation. It is the exception rather than the rule to have to make repeated tests. We should like to emphasize that to get a true basal rate in new patients their confidence must be secured, and all details of technic carefully carried out. The matter of complete rest and the postabsorptive state on the part of the patient are of the utmost importance. So too is the taking of the body temperature and the recognition of the elevations that fever may cause. No one should attempt to make metabolism determinations who is not familiar with the principles of calorimetry and the why and wherefore of each step in the procedure, and a clear understanding of the pitfalls that may occur.

The finding of subnormal rates is rather simpler. A rate probably cannot be lowered by extraneous factors. Low rates mean abnormal metabolism, they are not open to the possibility of being artefacts, as high rates are.

In general, we feel from the mass of data now in the literature as well as from our own experience that high rates mean hyperthyroidism,

12. Aub, J. C.; Bright, E. W., and Forman, J.: Metabolic Effect of Adrenalectomy on the Urethanized Cat, Am. J. Physiol. **61**:349 (July) 1922.

provided a few well recognized other causes for increased metabolism, leukemia, anemia, acromegaly, fever, etc., are ruled out, and that low rates mean hypothyroidism provided hypopituitarism, Addison's disease, starvation, etc., are ruled out. There seldom should be any great difficulty in excluding the conditions other than thyroid which alter the matabolic rate, they are few in number and present fairly obvious clinical signs.

CONCLUSIONS

1. Patients with an outspoken clinical picture of hyperthyroidism invariably show increased metabolism, and those with definite clinical pictures of hypothyroidism invariably show decreased metabolism. Those with goiters, but no signs or symptoms of abnormal thyroid function, for the most part show normal metabolism.

2. Patients with atypical or incomplete clinical evidence of abnormal thyroid function may show normal or abnormal metabolism. The majority show normal metabolism.

3. By inference from the indirect evidence we believe that in these borderline thyroid cases, provided that in the first place a true basal rate is secured, and, provided that certain well recognized causes for increased metabolism, such as fever, acromegaly, leukemia and severe anemia are excluded, the finding of an increased basal metabolic rate is strong presumptive evidence of hyperthyroidism. In a similar way, provided that such conditions as starvation, hypopituitarism, and hypo-suprarenalism are excluded, a low metabolic rate is strong presumptive evidence of hypothyroidism.

4. To that extent, then, the metabolism test is distinctly useful in differential diagnosis. Like all other laboratory tests it should only be interpreted with due regard to all other clinical and laboratory findings, and with due regard for its limitations and pitfalls.

We are indebted to Miss Catherine Thacher and Miss Margaret N. Woodwell for making a considerable number of the metabolism tests.

THE ALKALIMETRY OF WHOLE BLOOD

SECOND PAPER: THE ACID FIXING POWER OF THE BLOOD IN RENAL DISEASE *

JOHN B. RIEGER, M.D., AND HUGO A. FREUND, M.D.
DETROIT

Our present conception of the physiologic acid-base equilibrium, resting largely on the work of L. J. Henderson,[1] assigns to the kidney the principal rôle in maintaining the normal alkalinity of the body fluids. So adequate is the healthy kidney in this respect that the production of acid within the body may be increased to many times the basal amount, as, for example, during great muscular exertion and in the ketosis of diabetes mellitus, without sensibly reducing the bicarbonate content of the blood.

Indeed, from the work of Straub and Schlayer,[2] Lewis and his co-workers,[3] of Peabody,[4] Whitney,[5] MacNider,[6] Gettler and St. George,[7] Chace and Myers,[8] and others, it appears that no appreciable reduction of the blood bicarbonate occurs, until the function of the kidney, as determined by the conventional tests, has been affected gravely. Acidosis, defined as a condition of lowered blood bicarbonate, appears, then, to be of little importance in the diagnosis of renal insufficiency.

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* The first paper, "The Alkalimetry of Whole Blood—A Preliminary Study," by John B. Rieger, appeared in the J. Lab. & Clin. M. **5**:668 (July) 1920.

1. Henderson, L. J.: Das Gleichgewicht zwischen Basen und Säuren im tierischen Organismus, Ergebn. d. Physiol. **8**:254, 1909; A Critical Study of the Process of Acid Excretion, J. Biol. Chem. **9**:403, 1911; The Theory of Neutrality Regulation in the Animal Organism, Am. J. Physiol. **21**:427, 1908.

2. Straub, H., and Schlayer, K.: Die Urämie eine Säurevergiftung? München. med. Wchnschr. **59**:569 (March 12) 1912.

3. Lewis, T.; Ryffel, J. H.; Wolf, C. G. L.; Cotton, T., and Barcroft, J.: Observations Relating to Dyspnea in Cardiac and Renal Patients, Heart **5**:45 (Oct.) 1913.

4. Peabody, F. W.: Studies in Acidosis and Dyspnea in Renal and Cardiac Disease, Arch. Int. Med. **14**:236 (Aug.) 1914.

5. Whitney, J. L.: Studies on Acidosis; the Immediate Cause of Death, and Remarks on the Acidosis of Nephritis, Arch. Int. Med. **20**:931 (Dec.) 1917.

6. MacNider, DeB. Wm.: A Study of Renal Function and the Associated Disturbance in the Acid-Base Equilibrium of the Blood in Certain Experimental and Naturally Acquired Nephropathies, Arch. Int. Med. **26**:1 (July) 1920.

7. Gettler, A. O., and St. George, A. V.: The Value of Modern Blood Chemistry to the Clinician, J. A. M. A. **71**:2033 (Dec. 21) 1918.

8. Chace, A. F., and Myers, V. C.: Acidosis in Nephritis, J. A. M. A. **74**: 641 (March 6) 1920.

Hoesslin,[9] Sellards,[10] Palmer and Henderson,[11] however, from their studies of the effect of alkali administration on the reaction of the urine, concluded that a condition of acidosis exists in the incipient nephropathies as well as in a great variety of other pathologic conditions, and often occurs unexpectedly. This observation is in harmony with the findings of several earlier workers, who used a much cruder method of study—titrating the alkalinity of the blood directly, with tartaric acid and litmus paper. In 1878, Canard [12] noted that the alkalinity of the blood is increased following digestion and after ingestion of alkali; decreased, following the ingestion of large amounts of acid. In 1879, Lepine [13] reported a decreased alkalinity in chronic nephritis, gastric ulcer, diabetes mellitus, and the anemias, and in 1888 von Jaksch,[14] as the result of an extensive investigation, concluded that there is decreased alkalinity of the blood in every febrile process; that the decrease is constant in uremia, diseases of the liver which result in the destruction of tissue, and in the anemias.

Later, Palmer and Henderson [15] studied the acid and ammonia excretion in various nephropathies and noted a decrease in the total titratable acidity of the urine, most pronounced in late glomerular disease, yet also to be observed in the early glomerular and in the degenerative processes. They noted that the decrease was invariably due to an ammonia deficit, just as Adler and Blake [16] had observed that the amount of base excreted in the urine of dogs fed hydrochloric acid followed, in general, the variations in the amount of ammonia. Palmer and Henderson [17] concluded, therefore, that the true regulator of urinary acidity is to be found in the production of ammonia, a process which is "not always correlated with the other regulatory processes of the kidney." The regulation of the hydrogen ion concentration of the blood, they believed to depend almost entirely on the acid excretion.

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9. Hoesslin, V.: Ueber die Abhängigkeit der Albuminurie vom Säuregrad des Urin und über den Einfluss der Alkalizufuhr auf Azidität, Albuminurie, Diurese und Chloridausscheidung sowie auf das Harnammoniak, Deutsch. Arch. f. klin. Med. **105**:147, 1912.

10. Sellards, A. W.: The Determination of Equilibrium in the Human Body Between Acids and Bases with Especial Reference to Acidosis and Nephropathies, Bull. Johns Hopkins Hosp. **23**:289, 1912.

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12. Canard, J.: Essai sur l'alcalinité du sang dans l'état de sante et dans quelques maladies, Thèse II, Paris, 1878.

13. Lepine, R.: Note sur la Determination de L'alcalinite du Sang chez L'homme, Gaz. med. de Par. **12**:149 (March 23) 1878.

14. Von Jaksch, R.: Ueber die Alkalescenz des Blutes bei Krankheiten, Ztschr. f. klin. Med. **13**:350, 1888.

15. Palmer, W. W., and Henderson, L. J.: A Study of the Several Factors of Acid Excretion in Nephritis, Arch. Int. Med. **16**:109 (July) 1915.

16. Adler, H. M., and Blake, G.: The Retention of Alkali by the Kidney, with Special Reference to Acidosis, Arch. Int. Med. **7**:479 (April) 1911.

17. Henderson, L. J., and Palmer, W. W.: Intensity of Urinary Acidity in Normal and Pathological Conditions, J. Biol. Chem. **13**:393, 1913.

PHOSPHATE RETENTION AND RENAL FUNCTION

That acidosis may at times be due specifically to retention of acid phosphate is shown by the work of Greenwald,[18] Marriott and Howland,[19] Feigl,[20] Denis and Minot [21] and others. Greenwald found that the acid soluble phosphorus in nephropathies is increased roughly parallel with the nonprotein nitrogen, while the careful work of Denis and Minot showed a retention of inorganic phosphate by about 65 per cent. of the seventy nephropathic individuals studied, reaching ten times the normal value in fatal cases and, in general, closely following the condition of the patient. Marriott and Howland found the inorganic phosphates usually slightly increased in marked renal disease, though death occurred a number of times in such cases, without any increase of phosphorus and without any evidence of acidosis. In certain instances the phosphoric acid was found to be combined with twice as much of the available base as was the carbonic acid, whereas in normal conditions the base combined with phosphoric acid is only from one-tenth to one-fifteenth of that combined with carbonic acid. In mild cases in which the nitrogen retention and the phenolsulphonephthalein elimination were not markedly affected, no phosphate retention was observed.

The excretion of acid phosphate by the normal kidney is stimulated, apparently, in all conditions in which acid tends to accumulate in the body fluids. Thus, Fitz, Alsberg and Henderson [22] and later, Underhill and Bogert [23] found an increased elimination of phosphates in rabbits fed with hydrochloric acid. Underhill and Bogert [24] also noted that diets producing acid urines in these animals increased the elimination of phosphates through the kidney, while diets producing alkaline urines forced a greater elimination by gut, an observation that has been made on a great variety of animals by other workers and which

18. Greenwald, I.: The Estimation of Lipoid and Acid Soluble Phosphorus in Small Amounts of Serum, J. Biol. Chem. **21**:29, 1915.

19. Marriott, W. McK., and Howland, J.: Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, Arch. Int. Med. **18**:708 (Dec.) 1916.

20. Feigl, J.: Ueber das Vorkommen von Phosphaten im menschlichen Blutserum, Biochem. Ztschr. **83**:218 (Oct.) 1917; Biochemische Untersuchungen über den Einfluss von Marschanstrengungen auf die Zusammensetzung des Blutes, ibid. **84**:332 (Dec.) 1917.

21. Denis, W., and Minot, A. S.: Study of Phosphate Retention from the Standpoint of Blood Analysis, Arch. Int. Med. **26**:99 (July) 1920.

22. Fitz, R.; Alsberg, C. L., and Henderson, L. J.: On the Intensity of Urinary Acidity in Normal and Pathological Conditions, Am. J. Physiol. **18**: 113, 1907.

23. Underhill, F. P., and Bogert, L. J.: Urinary Excretion of Phosphates in the Rabbit, J. Biol. Chem. **36**:521 (Dec.) 1918.

24. Underhill, F. P., and Bogert, L. J.: Alterations in the Output of Certain Urinary Constituents as Determined by Changes in the Character of the Diet, J. Biol. Chem. **27**:161, 1916.

probably forms the basis for the milk treatment of renal insufficiency as it is practiced today. When injected subcutaneously into rabbits Underhill and Bogert recovered from 70 to 100 per cent. of the phosphate in the urine and the increment of excretion was no greater with the monobasic than with dibasic and tribasic salts. There was found, however, a wide variation in the ability of individual rabbits to excrete phosphates through the kidney, and it is possible that a similar variation in ability to excrete phosphates occurs among humans, and that the phosphate content of the body fluids of the latter may, in some cases at least, be profoundly modified by the action of the bowel.

The effect of acid phosphate retention on renal function is illustrated by the work of Nagayama,[25] who fed to rabbits molecularly equivalent amounts of phosphorus as acid phosphate and as basic phosphate, respectively, and was able to show that the urea excretory activity of the kidney is distinctly depressed after the former, while the latter had no appreciable effect. Sodium bicarbonate in amount markedly increasing the alkalinity of the plasma caused only a slight decrease in this function.

ACID RETENTION AND RENAL FUNCTION

It has long been maintained, notably by Fischer,[26] that an abnormal production of acid in the body and accumulation in the kidney is responsible for the entire symptom complex known as nephritis. To the action of the retained acid on the colloidal structures that make up the kidney are due, in his opinion, the specific morphologic changes, the proteinuria, the production of casts, etc., and on theoretic grounds could as well be initiated by retention of alkali. Newburgh,[27] and Newburg and Squier,[28] also state that they have been able to reproduce in the rabbit all the anatomic changes characteristic of the chronic interstitial nephropathy in man, merely by feeding protein in amounts sufficient to increase the urinary nitrogen from 2 to 300 per cent. They, however, made no attempt to correlate their findings with any specific product of protein metabolism, so that it cannot be said whether the increased acid production that must result from such diets was or was not a causative factor.

Of the conditions that govern the excretion of acid by the kidney, little is known. If, as stated by Henderson, this organ is the first line of defense against an accumulation in the body fluids of acid or alkaline

25. Nagayama, T.: The Urea Excreting Activity of the Kidney and Phosphate Excretion, Am. J. Physiol. **51**:449 (April) 1920.

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28. Newburgh, L. H., and Squier, T. L.: High Protein Diets and Arteriosclerosis in Rabbits, A Preliminary Report, Arch. Int. Med. **26**:38 (July) 1920.

substances beyond the physiologic optimum, the first indication of its functional lag should, it seems, be found in the acid or alkali binding power of the blood.

The acid binding power of the blood, for convenience designated "oxydesis," may be altered by processes occurring without, as well as within the kidney. In the early stages of diabetes mellitus, for example, oxydesis is definitely increased, and according to Michaelis [29] and to Menten,[30] the H ion concentration of the serum is lowered, while in the later stages, when there is considerable ketone formation, oxydesis is notably decreased, and, according to the same observers, the H ion concentration rises. This may be explained, perhaps, entirely by variations in the ratio of ammonia to acid formed, or it may be due to a preferential retention by the kidney of the stronger fixed bases, the complete elimination in the early stages of acid ammonium salts and later their gradual accumulation because of renal lag.

Since the H ion concentration of the blood depends on the ratio of acid to alkali, the determination of the alkali reserve, indirectly by measuring the bicarbonate bound carbon dioxid of the plasma, or directly by one of the various forms of alkalimetry, cannot serve as an infallible index of acidosis or alkalosis. Thus, Henderson and Haggard,[31] Van Slyke,[32] and Henderson, Haggard and Coburn [33] describe nine theoretically possible combinations of acidosis, alkalosis and normality, by the plasma bicarbonate index, with a high, low and normal alkali reserve, several of which they have clinically observed in conditions where occur such abnormalities of respiration as hyperpnoe and acapnia.

The combination of carbonic acid deficiency and high alkali reserve, we ourselves have observed in diabetic coma of the rapidly advancing type, the oxydesis here being moderately decreased, normal or actually increased, in the face of a plasma bicarbonate content always below twenty volumes per cent. In the nephropathies, however, except when uremia or cardiac decompensation impends, there are, as a rule, no respiratory complications and there is no increased production of acid or alkali. An interesting exception is a condition designated paroxysmal

29. Michaelis, L.: Die Wasserstoffionen Konzentration, Berlin, 1914.

30. Menten, M. L.: The Alkalinity of the Blood in Malignancy and Other Pathological Conditions, Together with Observations on the Relation of the Alkalinity of the Blood to Barometric Pressure, J. Cancer Res. **2**:179 (April) 1917.

31. Henderson, Y., and Haggard, H. W.: Hematorespiratory Functions, J. Biol. Chem. **39**:163 (Aug.) 1919; **43**:3, 15 (Aug.) 1920; **47**:421 (July) 1921.

32. Van Slyke, D. D.: Studies in Acidosis; Normal and Abnormal Variations in Acid-Base Balance of Blood, J. Biol. Chem. **48**:153 (Sept.) 1921.

33. Henderson, Y.; Haggard, H. W., and Coburn, R. C.: The Therapeutic Use of Carbon Dioxid after Anesthesia and Operation, J. A. M. A. **74**:783 (March 20) 1920.

probably forms the basis for the milk treatment of renal insufficiency as it is practiced today. When injected subcutaneously into rabbits Underhill and Bogert recovered from 70 to 100 per cent. of the phosphate in the urine and the increment of excretion was no greater with the monobasic than with dibasic and tribasic salts. There was found, however, a wide variation in the ability of individual rabbits to excrete phosphates through the kidney, and it is possible that a similar variation in ability to excrete phosphates occurs among humans, and that the phosphate content of the body fluids of the latter may, in some cases at least, be profoundly modified by the action of the bowel.

The effect of acid phosphate retention on renal function is illustrated by the work of Nagayama,[25] who fed to rabbits molecularly equivalent amounts of phosphorus as acid phosphate and as basic phosphate, respectively, and was able to show that the urea excretory activity of the kidney is distinctly depressed after the former, while the latter had no appreciable effect. Sodium bicarbonate in amount markedly increasing the alkalinity of the plasma caused only a slight decrease in this function.

ACID RETENTION AND RENAL FUNCTION

It has long been maintained, notably by Fischer,[26] that an abnormal production of acid in the body and accumulation in the kidney is responsible for the entire symptom complex known as nephritis. To the action of the retained acid on the colloidal structures that make up the kidney are due, in his opinion, the specific morphologic changes, the proteinuria, the production of casts, etc., and on theoretic grounds could as well be initiated by retention of alkali. Newburgh,[27] and Newburg and Squier,[28] also state that they have been able to reproduce in the rabbit all the anatomic changes characteristic of the chronic interstitial nephropathy in man, merely by feeding protein in amounts sufficient to increase the urinary nitrogen from 2 to 300 per cent. They, however, made no attempt to correlate their findings with any specific product of protein metabolism, so that it cannot be said whether the increased acid production that must result from such diets was or was not a causative factor.

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dyspnea or "renal asthma," in which there is a nocturnal anaphylactoid suppression of urine with profound dyspnea, superimposed on what could otherwise be diagnosed a chronic interstitial nephropathy.

Whatever be the significance of an increase in the acid fixing power of the blood, a decrease, whether it occur in a nephropathy, in anemia, diabetes mellitus, inanition, ileus, pneumonia or gastric ulcer, and whether it exist as cause or effect thereof, must with great frequency, if not always, be associated with a lag or impairment of renal function. That it is a measure of such impairment cannot be affirmed, for, as was previously stated, it is possible that in a chronic nephropathy the resorptive activity of the bowel may greatly increase, and measurably subserve the function of the kidney.

THE ALKALIMETRY OF WHOLE BLOOD

The acid binding power, or oxydesis, of whole blood may be determined as described in the first paper of this series and for the purpose of this investigation represents the greatest amount of hundredth normal hydrochloric acid that can be added to a unit volume of oxalated whole blood without clumping the erythrocytes. For convenience the method is here repeated:

Ten clean dry test tubes are set up in a rack. To the first is added 9 c.c. of an 0.85 per cent. salt solution (Merck's blue label sodium chlorid dissolved in freshly distilled water) and 1 c.c. whole, fresh oxalated blood. A 1 c.c. differential bacteriologic pipet may be used for the purpose. The blood is mixed with the saline by blowing through the pipet, and froth is avoided by always keeping the tip of the pipet below the surface of the liquid. One cubic centimeter of the diluted blood is then carefully placed in the bottom of each tube, avoiding the sides, and starting on the left, hundredth normal hydrochloric acid containing 0.85 per cent. chemically pure sodium chlorid is added with a 2 c.c. differential pipet, starting with 0.7 c.c., and increasing the amount by 0.05 c.c. with each tube. The tip of the pipet should be poised about 2 inches above the surface of the fluid, to insure rapid diffusion of the acid, which should be dropped directly into the blood and not be touched off on the glass. The tube, once charged, should be shaken immediately, and the row not disturbed until the corpuscles have settled. The last tube which shows the erythrocytes sharply settled in the center without any hemolysis in the supernatant liquid represents the oxydetic value of the blood in question.

The blood should be collected not less than three hours after ingestion of food, in 1 ounce salt mouth bottles, to which 1 c.c. of a 1 per cent. solution of recrystallized, chemically pure sodium oxalate has been added and evaporated to dryness. This amount is sufficient for 10 c.c. blood, which should be swirled around the bottle immediately on collection. Failure to observe this precaution will result in more or less agglutination of the corpuscles such as always occurs previous to coagulation (blood containing no anticoagulant may be used if one is in a position to dilute it immediately with nine volumes of physiologic solution of sodium chlorid). The syringe and needle should be dry and clean and the blood should be used immediately or placed in a good icebox, where it will keep for twenty-four hours. It should be brought to room temperature before measuring.

Whether the figure obtained in this way represents accurately the buffer content or tampon power of the blood for acid, cannot be stated. It is not known, for example, to what extent the blood-proteins are

available to physiologically fix acid; whether this fixation is a stoichiometric one or whether, as MacLeod [34] states, it is conditioned by the H ion concentration of the blood and becomes greater as the latter increases. The figures obtained will also vary because of differences in calibration of glassware, standardization of acid and, perhaps, a personal factor. The absolute oxydetic values are, however, of little clinical importance. If the same acid and the same pipet be used for the samples of blood that it is desired to compare, it will be found that the amount of acid that can be added to a unit volume of normal blood without clumping the erythrocytes is, for practical purposes, a constant.

Fifty individuals, for example, ranging in age from 19 to 52 years and whose blood and urine were found to be normal, showed an acid fixing power of from 8.5 to 9.5 c.c. of hundredth normal hydrochloric acid per 1 c.c. of whole oxalated blood. Forty-eight of these gave a figure of 90, one, 85 and one, 95, three hours after ingestion of food. Whether a figure below 90 consistently indicates a nephropathy or a low renal reserve is the object of this study; and during the past two years, alkalimetry was performed on all patients whose blood and urinary findings suggested a nephropathy and for comparison in many cases in which other diagnoses had been made.

OXYDESIS IN THE NEPHROPATHIES

The nephropathies of vascular origin were, for the purpose of this study, grouped according to the amount of nitrogen retention shown upon first examination. Group 1 comprised those patients in whom hypertension was the sole finding. Group II showed in addition to hypertension, a retention of nitrogen, and Group III showed hypertension, nitrogen retention and fixation of the specific gravity of the urine. None of the patients of the last group were alive six months after the date of examination. That the parenchymal involvement in these cases was minimal is assumed because there was no history of edema, and none was ever observed.

The nephropathies that were deemed to be predominantly parenchymal in type were, for fault of a better classification, simply regarded as early or late cases, forming Groups IV and V, respectively. Nearly all the patients in these groups had more or less edema, their systolic blood pressures were, as a rule, not high and they were, on an average, much younger than the patients of Groups I, II, and III.

Group VI comprised individuals on whom a definite diagnosis of nephropathy could not be made, in spite of proteinuria, edema or other suggestive symptoms.

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34. MacLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, Ed. 3, 1920, St. Louis, C. V. Mosby Co., p. 41.

Group VII was composed of what were considered primary cardiac cases characterized by dyspnoea with cyanosis, feeble irregular pulse, subnormal blood pressure and minimal renal involvement.

The nonprotein nitrogen was determined by the tungstic acid precipitation method of Folin and Wu,[35] and in the same filtrate the chlorids were titrated by the Volhard method adapted thereto by Rieger.[36] The bicarbonate bound carbon dioxid was determined by the gasometric method of Van Slyke.[37]

DISCUSSION OF RESULTS

Analysis of Tables 1, 2 and 3 reveals little tendency toward accumulation of acid in the nephropathies of vascular type, until a few months before death, when oxydesis may be definitely decreased. These patients do not, as a rule, die of acidosis, nor uremia, but of heart failure and although the nonprotein nitrogen of the blood increases steadily up to hundreds of milligrams per hundred cubic centimeters, the phenolsulphonephthalein excretion drops to zero, and the blood chlorids maintain a high level, oxydesis, in the last few days of life, may increase. Patients M.D. and C.S. in Group III show this tendency to a minor degree, while patient 7,634, Group VII, shows it markedly—oxydesis in the latter instance having been 105 at the time of death. This patient was transferred from the class of vascular nephropathies to that of predominant cardiac disease, because of falling blood pressure, and oxydesis rose from 80 to 105, within four months.

Patients with marked cardiac involvement have not as a rule shown low oxydesis and the advanced cases cited in Group VII show an acid fixing ability definitely above normal. This is possibly due to mobilization in the blood stream of alkali to equilibrate the carbonic acid retained through dyspnea.

In the diffuse nephropathies forming Groups IV and V oxydesis is definitely decreased from the onset, acid being retained along with salt, and less constantly, water, before there is any retention of nonprotein nitrogen or phenolsulphonephthalein. The low figures obtained in patients D.R.H.-S. and H.H.-N., both for oxydesis and blood bicarbonate carbon dioxid, and in both instances within a few hours of death, indicated that they died in acidosis, but that does not mean that they died of acidosis, for D.R.H.-D showed the same low figures two months before death, and D.R.H.-S. never had an oxydesis higher than

35. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

36. Rieger, J. B.: The Estimation of Chlorids in Whole Blood, J. Lab. & Clin. M. **6**:44 (Oct.) 1920.

37. Van Slyke, D. D.: A Method for the Determination of Carbon Dioxid and Carbonates in Solution, J. Biol. Chem. **30**:347, 1917.

TABLE 1.—Group I. Hypertension

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenol-sul-phone-phthal-ein	Oxydesis	Plasma Bicar-bonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp. Gr.	Protein	Sediment	
H. H.-P	12	250-170	28	90	90	68	462	.....	s. p. t.	None	Probably the acute interstitial nephritis of Councilman
9110	52	280-140	30	45	90	55	453	1.005-1.022	s. p. t.	Occ. hyaline cast	Probable duration 8 years
7869	33	165-110	27	85	90	58	480	1.010-1.032	None	None	Duration less than 1 year
7283	51	300-170	29	..	90	..	...	1.012-1.030	s. p. t.	Occ. casts and r. b. c.	Symptoms began 1 year ago
8654	50	200-120	27	70	90	61	450	1.005-1.012	s. p. t.	Occ. cast	Duration more than 5 years

TABLE 2.—Group II. Hypertension with Retention of Nitrogen

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenol-sul-phone-phthal-ein	Oxydesis	Plasma Bicar-bonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp. Gr.	Protein	Sediment	
6068	49	202-130	40	20	90	54	453	1.006-1.022	s. p. t.	None	Duration at least 2 years; no nyctaluria
8262	66	160- 90	39	60	85	55	450	1.010-1.020	None	Occ. hyaline cast	Sole symptom, nyctaluria 1-2 years
8120	49	250-150	34	45	80	58	460	1.005-1.012	s. p. t.	Occ. hyaline case	Duration less than 4 years, marked arteriosclerosis
8924	67	230-100	37	75	90	57	...	1.005-1.016	s. p. t.	Rare hyaline casts	Senile myocarditis; arterio sclerosis
1402	49	202-130	34	40	85	60	472	1.012-1.008	s. p. t.	Rare cast	Blood pressure above 150 systolic for 10 years

TABLE 3.—Group III. Hypertension, Nitrogen Retention and Fixation of Urinary Specific Gravity

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenol-sul-phone-phthal-ein	Oxydesis	Plasma Bicar-bonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp. Gr.	Protein	Sediment	
7770	50	235-135	63	15	60	42	555	1.018-1.020	+++	Many casts	Died in 3 months, heart failure
8629	67	240-135	75	20	70	40	...	1.008-1.010	++	Frequent casts	Died in 1 month, heart failure
8797	51	260-165	42	68	65	45	500	1.020-1.022	++++	Many casts	Died in 3 months, uremic coma
C-McD.	50	260-150	75	..	75	..	513	1.010-1.011	++	Occasional casts	Orthopnea, irregular cardiac rhythm; died in 6 months
9253	50	300-160	45	55	75	52	525	1.018-1.022	++	Occasional casts	Irregular cardiac rhythm, alive 1 month later
M-D.	48	180- 0	150	0	80	68	547	1.009-1.011	++++	Frequent hyaline casts	Died in 3 hours, heart regular to end, pendant edema, aortic disease
C-S.	47	180-120	275	..	85	72	530	1.012	+++	.....	Died in 1 hour, no edema, heart regular

TABLE 4.—Group IV. Early Diffuse Nephropathies

Case	Age	Blood Pressure	Non-protein Nitro-gen	Phenol-sul-phone-phthal-ein	Oxydesis	Plasma Bicar-bonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp. Gr.	Protein	Sediment	
9170	28	118-75	28	..	80	51.2	530	1.022	+	None	Edema of feet and ankles; erythema nodosum
D. R. H.-B.	16	140-95	38	15	65	57.4	557	1.012-1.015	+++	Many hyaline and granular casts	Acute nephritis with recovery in 1 month, general edema of face, arms and hands
7712	36	115-75	34	46	70	48.1	555	1.022-1.025	+++	Occ. hyaline casts, frequent r. b. c.	Severe secondary anemia; edema of legs, enteritis
9009	20	120-80	29	60	80	62.2	519	1.028	+	None	Malaise, lassitude, sole complaint
8029	19	105-85	28	..	75	....	...	1.032	++++	Considerable blood, no casts	Beginning of an acute hemorrhagic nephritis; early pulmonary tuberculosis

TABLE 5.—Group V. Chronic Diffuse Nephropathies

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenol-sul-phone-phthal-ein	Oxydesis	Blood Bicar-bonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp. Gr.	Protein	Sediment	
5308	42	132-100	35	40	70	53.0	510	1.025-1.030	++	Frequent hyaline casts	Edema of feet for 2 years
7383	33	124- 80	42	75	60	42.3	575	1.003-1.010	++	Considerable pus, Occ. casts	Pyonephrosis, edema of face and extremities for 1 year
7382	5 months later	130- 85	35	..	60	48.7	553	1.001-1.015	++	Much pus	Had been on low nitrogen and low salt diet
H. H.-N.	48	.....	160	0	40	12.5	...	.....	++++	.....	Moribund; necropsy: large white kidneys
6302	42	122- 70	66	20	55	....	...	1.005-1.015	++++	Waxy, fatty epithelial casts	Amyloid disease; persistent slight edema 3 years
6302	6 months later	.....	46	..	50	35.6	...	.....	++++	.....	Died in 3 months
D. R. H.-K	28	200-100	41	..	70	55.0	500	1.030-1.028	++++	Many hyaline and granular casts	Uremic convulsion with recovery in 1 month
D. R. H.-D	26	155-100	95	25	45	16.3	545	1.015-1.020	++++	Many hyaline and granular casts	General anasarca; died 2 months later, necropsy; large white kidneys
3150	16	125- 80	32	50	80	66.5	550	1.010-1.020	+++	Tubular casts frequent	Four years duration, no localized edema, pasty appearance
D. R. H.-R.	35	132- 90	33	..	80	55.4	505	1.006-1.026	+++	Few granular casts	Edema of legs, third admission to hospital in 1 year
D. R. H.-S	40	185-115	55	5	45	15.6	582	.....	++++	Many granular casts	Died in 1 hour; necropsy: large white kidneys

TABLE 6.—Group VI. Renal Disease Suspected

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenol-sul-phone-phthal-ein	Oxydesis	Blood Bicar-bonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp. Gr.	Protein	Sediment	
8660	19	.....	28	..	75	47.5	478	1.022	++	Nothing	Suspected mediastinal tumor, edema of face and neck, prominent thoracic veins
8160	34	130- 84	25	..	80	....	462	1.030	++	Occ. casts; frequent pus cells	Attacks of transient, unilateral amaurosis
8622	27	120- 80	28	55	80	72.4	470	1.020	+	Occ. casts	Diffuse edema of arms and hands, urticaria
9061	42	118- 85	30	72	75	52.2	505	1.005	+	Frequent granular casts, many r. b. c.	Furunculosis, sole complaint; temperature 99.6; beginning hemorrhagic nephritis
8231	25	128- 80	27	80	80	68.3	495	1.010-1.030	++	No casts	Malaise, lassitude, pallor
J. F., nurse	36	120- 84	27	..	80	66.5	452	1.028	+	Occ. mucus shreds	No complaint, frequent puffiness of lower eyelids
7602	37	98- 70	32	74	80	60.2	461	1.030	0	Nothing	Strong appearing mechanic; easily fatigued; nocturia II, 7-8 years
8641	45	175-110	30	..	75	....	...	1.008-1.025	0	Nothing	Subacute arthritis, shortness of breath
8645	17	130- 90	29	78	85	....	...	1.010-1.018	+	Nothing	Feet swollen for several years, headache, backache, lassitude

TABLE 7.—Group VII. Predominant Cardiac Disease

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenol-sul-phone-phthal-ein	Oxydesis	Blood Bicar-bonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp. Gr.	Protein	Sediment	
9082	54	.....	32	77	100	84	...	1.020-1.030	+	None	Mitral stenosis, pulse 128, irregular; no edema, cyanosis
8374	55	.....	55	82	100	78	...	1.028	++	Frequent hyaline casts	Pendant edema, dyspnea; cyanosis
7634	57	160-105	50	..	85	72	...	1.030	++	Frequent hyaline casts	Heart sounds weak, râles throughout chest
7634	5 weeks later	160- 90	37	..	80	..	...	1.030	+++	Many hyaline casts	Orthopnea, pulse 100
7634	4 months later	120- 90	40	..	105	86	452	1.018	+	Frequent hyaline casts	Auricular fibrillation; death in 3 days, cyanosis
7223	60	.....	37	75	105	82	...	.....	+++	Very many casts	Auricular fibrillation; pendant edema, dyspnea, cyanosis

50 or a bicarbonate carbon dioxid higher than twenty-four volumes per cent. during his entire stay of one month in the hospital. At necropsy each of these patients showed bilateral large white kidneys.

Finally, there is a large group of patients whose symptoms suggest renal disease, yet in whom the sole evidence of functional impairment is decreased oxydesis. Some of these are included in Group VI. Nearly all show proteinuria, one or two show beginning retention of chlorids, and three or four show a slight edema.

An oxydetic value below 9 c.c. hundredth normal hydrochloric acid per cubic centimeter blood seems, then, to be an early and constant sign of renal insufficiency, and in all likelihood is due to parenchymal disease. Retention of acid in the diffuse nephropathies apparently precedes the retention of salt and water and is closely related thereto, while the retention of nonprotein nitrogen apparently does not occur until secondary contraction has begun, or in the acute cases, when there is marked oliguresis.

By the same token, the retention of nonprotein nitrogen is the earliest sign of insufficiency in the vascular type of nephropathy—the primarily contracted kidney, but owing to the great glomerular reserve of the organ, retention of acid, chlorids and water does not occur until very late in the disease.

Given, then, hypertension, breathlessness and edema, alone or in association, oxydesis should serve as a gage of the distribution of disease between the vascular bed and parenchyma of the kidney, and in the later stages, as a relative measure of cardiac and renal sufficiency. Thus a figure of 75 or above, with the symptoms mentioned, would mean predominant vascular disease, while lower figures would indicate predominant parenchymal disease. A figure of 85 or more, together with breathlessness, would be taken as an indication of impending heart failure.

The occurrence of decreased oxydesis in conjunction with such vague symptoms as malaise, lassitude, pallor, slight proteinuria or transient localized edemas, alone or in combination, demonstrates the possibilities of alkalimetry in the diagnosis of early diffuse nephropathies.

Indeed, in our experience, a decreased oxydesis is the earliest and most constant sign of renal insufficiency. What may be its exact significance cannot be stated. The work of Nash and Benedict[38] indicates that the kidney is a seat of ammonia formation, and Palmer and Henderson have shown quite conclusively that there is, in the various nephropathies, a deficit in the output of urinary ammonia, bound with fixed acid. That certain ammonium salts retained by a damaged

38. Nash, T. P. Jr., and Benedict, S. R.: The Ammonia Content of the Blood and Its Bearing on the Mechanism of Acid Neutralization in the Animal Organism, J. Biol. Chem. **48**:463 (Oct.) 1921.

kidney can function as acid in degree sufficient to appreciably lower the alkali reserve, is exceedingly doubtful. It is more logical to argue that the lesion which damages the acid excreting function of the kidney damages the ammonia producing function as well.

SUMMARY

1. The greatest amount of acid that may be added to a unit volume of whole blood without agglutinating its erythrocytes is taken as the acid binding value of that blood. It is designated "oxydesis."

2. Oxydesis in health and in the postabsorptive state is for practical purposes a constant. For 1 c.c. whole blood, oxalated as described, it is approximately equivalent to 9 c.c. hundredth normal alkali.

3. Oxydesis, below ninety (0.9 c.c. hundredth normal hydrochloric acid per 0.1 c.c. blood) appears to be an early and constant sign of renal insufficiency when due to a glomerular lesion.

4. In the diffuse nephropathies oxydesis is definitely increased before there is retention of water, chlorids, or phenolsulphonephthalein and long before there is nitrogen retention.

5. In the degenerative vascular nephropathies, there is retention of nitrogen before there is retention of chlorids, water or phenolsulphonephthalein, and oxydesis is not definitely decreased until the late stages.

6. In cardiorenal disease, with preponderant cardiac involvement, oxydesis is normal, and in the late stages increased.

7. In cardiorenal disease, oxydesis serves as a rough gage of the relative involvement of heart and kidney.

8. Decreased oxydesis signifies a decreased alkali reserve, either because of an accumulation of acid, deficient production of ammonia or both.

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